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Familial rare EGFR-mutant lung cancer syndrome: Review of literature and description of R776H family

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ABSTRACT

Background: Interest in hereditary lung cancer is increasing, in particular germline mutations in the Epidermal Growth Factor Receptor (*EGFR*) gene. We review the current literature on this topic, discuss risk of developing lung cancer, treatment and screening options and describe a family of 3 sisters with lung cancer and their unaffected mother all with a rare EGFR germline mutation (EGFR p.R776H).

Methods: We searched PubMed, Medline, Embase, the Cochrane Library, Google Scholar and scanned reference lists of articles. Search terms included "EGFR germline" and "familial lung cancer" or "EGFR familial lung cancer". We also describe our experience of managing a family with rare germline *EGFR* mutant lung cancer.

Results: Although the numbers are small, the described cases in the literature show several similarities. The patients are younger and usually have no or light smoking history. 50% of the patients were treated with a tyrosine kinase inhibitor (TKIs) with OS over six months.

Conclusion: Although rare, germline p.R776H EGFR lung cancer mutations are over-represented in light or never smoking female patients who often also possess an additional somatic EGFR mutation. Treatment with TKIs appears suitable but further research is needed into the appropriate screening regime for unaffected carriers or light/never smokers.

1. Introduction and background

Lung cancer is the third most common type of cancer diagnosed in the UK [1] and is associated with significant morbidity and mortality, despite recent advances with immune and targeted therapies. Although the most common risk factors for lung cancer are smoking and air pollution [2], there is increasing awareness of the role that heritable genetic variation plays in oncogenesis.

Published linkage analysis and genome-wide association studies have identified candidate lung cancer susceptibility loci [3,4]. A pooled analysis from the International Lung Cancer Consortium by Cote et al (2012) showed that individuals with a family history of lung cancer had an increased risk of the disease, reporting odds ratios (OR) from 1.51 to 2.79 [5]. However, the studies included in the analysis were unselective for smoking related and unrelated lung cancer and were largely in an elderly population.

In a more recent case control study carried out amongst Chinese women in Singapore, Yin et al (2021) reported that a positive family history of lung cancer was found more frequently amongst patients with lung cancer, than in a matched control group [6]. The influence of a positive family history was particularly seen amongst never or light smokers (less than or equal to 5 cigarettes per day).

Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein with cytoplasmic kinase activity that can transduce essential growth factor signals from extracellular cues to cellular responses, which allows it to regulate cellular proliferation, differentiation, angiogenesis and metastasis [7]. EGFR is encoded by the *EGFR* gene, located on chromosome 7. Somatic variants in this gene in non-small-cell lung cancer were described for the first time in 2004 [7] and mainly occur in exons 18–21 which encode the intracellular tyrosine kinase domain of EGFR. Globally, variants in *EGFR* are found in 12 % of lung cancers and predict response to treatment with tyrosine kinase

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inhibitors [8]. The most common (also known as classic or sensitizing) *EGFR* variants are in-frame deletions in exon 19 and L858R substitution-missense (858: L – R) in exon 21 [8].

There are reported cases of families with clusters of lung cancer diagnoses, who have been found to share a particular constitutional predisposing variant. There have been challenges in establishing the contribution of such variants to lung cancer risk, particularly in those families where shared environmental risk factors co-exist. Gazdar et al (2014) reported a germline variant in *EGFR*: c.2369C > T (p.Thr790Met), hereafter referred to as T790M, through five generations of the same family [9]. The proband was a 29-year-old patient with a 4.4 cm left upper lobe adenocarcinoma. A somatic L858R (exon 21) variant was identified in her tumour as well as the familial T790M constitutional variant. After genetic counselling, eight out of the 17 unaffected family members tested were also found to carry the familial T790M variant. The associated lifetime risk of lung cancer in carriers of constitutional T790M variant has been estimated to be approximately 31 % in never or light smoking carriers [9]. Furthermore, Oxnard et al (2023) also report cases of extrapulmonary primary cancers in affected siblings of carriers of constitutional T790M [10].

The most common germline variant is the pathogenic T790M however there is a growing number of reports about rare but possibly significant alternative variants in *EGFR*, including R776H variants. Oxnard et al (2023) also reported *EGFR* T790M as a founder event in South East United States based on a prospective study of familial *EGFR* adenocarcinoma [10].

Constitutional pathogenic variants in other genes have been identified in patients with lung cancer, although causality has not been proven in all cases. It has been suggested that approximately 1 % of patients with NSCLC carry heterozygous germline variants in the *EGFR* gene [10]; the general population prevalence of such variants is likely to be much smaller [11].

In this review article, we explore the current published literature regarding familial rare EGFR-mutant lung cancer as well as discussing a family treated at our hospital, with three carriers of a familial constitutional variant in *EGFR* c.2327G > A (p.Arg 776His), hereafter referred to as R776H, developing lung cancers harboring a somatic additional hit - *EGFR* c.2156G > C (p.Gly719X), hereafter referred to as G719X.

2. Methods

2.1. Literature review

We searched PubMed, Medline, Embase, the Cochrane Library, Google Scholar and scanned reference lists of articles. Search terms included “EGFR germline” and “familial lung cancer” or “EGFR familial lung cancer”.

2.2. Family case report

In addition, we add to this literature by reporting the cases of three sisters who all developed lung cancers with an uncommon somatic *EGFR* mutation at a young age (<45 years). On germline genetic testing, they were all found to carry a rare constitutional *EGFR* variant, in *EGFR* R776H, which was found to be inherited from their unaffected mother.

3. Index patient (patient 1)

The index patient (Patient 1) was a fit and healthy, 37-year-old white British woman who presented with chest pain and a small pleural effusion during pregnancy in June 2015. She had a minimal smoking history of 5 pack years and stopped age 23. After delivery, Patient 1 underwent investigations including lung and pleural biopsies in July 2015 which demonstrated adenocarcinoma of lung origin. No mutations were detected on cell free DNA (Cobas 480), but testing using tumour-derived DNA identified an *EGFR* variant at G719. The technology applied (Cobas 480) could not distinguish between p.G719S/A/C. Staging after surgical resection was pT2a pN1 pM1a (pleural surface). She started afatinib which she continued until October 2017 when she was switched to Osimertinib due to unacceptable toxicity. In April 2018 she began second line carboplatin and pemetrexed due to disease progression. The new pleural effusion and lung nodules were found to carry the same *EGFR* mutation as the original tumour (p.G719A Exon 18) as well as a new T790M. In March 2019 Patient 1 was switched to atezolizumab (PDL1 > 50 %) for progressive disease but, unfortunately, continued to progress until June 2019 when she died from overwhelming cancer – 4 years from diagnosis.

4. Patient 2

Patient 2 is the middle sister of the three. She had minimal smoking history (2.5 pack years). She was 41 years old when she developed pain in her left shoulder in February 2017 and eventually had a CT scan. This demonstrated multiple ground glass opacities throughout both lungs, largest in the right upper lobe. Surgical biopsy of these lesions showed invasive adenocarcinoma of the lung, also positive for *EGFR* G719X as well as an additional *EGFR c.2582 T > A (p.Leu861Gln)*, hereafter referred to as L861Q mutation (exon 21). No mutations were detected in circulating DNA in blood (COBAS 480). The staging at diagnosis was T4 N0 M1a.

She started afatanib in July 2017 and continues on this treatment with no disease progression, 6 years since the diagnosis.

Patient 2 was also found to carry a variant in *BRCA2* (c.7939C > G, p.(Leu2647Val).

5. Patient 3

Patient 3 is the eldest of the three sisters. She elected to undergo a screening CT in June 2017 given her family history. She was 43 at the time and asymptomatic. She had an 8-pack-year smoking history and stopped smoking when she was in her 20 s. The CT showed suspicious lung nodules and she subsequently underwent surgical biopsies and resection of some of nodules which showed an invasive adenocarcinoma. Staging at diagnosis was T4 N0 M1A (pleural and contralateral lung). Genetic testing was performed on tumour-derived DNA, which identified the same variants identified in the tumour of her youngest sister: *EGFR* G719A, *EGFR* L858R and *EGFR* L861Q.

This patient started afatanib in September 2017 and her disease has been stable on this treatment 5.5 years since the diagnosis.

6. Constitutional genetic testing

All three were referred for germline genetic testing in July 2017. At that time, and at the time of writing, they were not eligible for NHS-funded tests so privately funded panel-based tests were undertaken for each patient.

All three sisters were found to carry a heterozygous variant in *EGFR*: c.2327G > A (Arg 776His). The *EGFR* G719X variant was not identified in the germline, consistent with somatic origin. Several additional variants of uncertain significance (VUS) were identified, which were not suspicious in terms of contribution to lung cancer risk. Review of the data from tumour-derived DNA analysis following this result demonstrated the presence of the R776H variant in the tumours of all 3 sisters, which had not been reported at the time of testing, because of its presence in paired germline-tumour analyses – the process of substraction used at the time.

To determine inheritance, testing in the parents of the patients found the variant to be maternally inherited. Radiological investigation has not identified any lung abnormalities in the mother to date. There was no significant family history of lung cancer. Their father has a history of low-grade prostate cancer.

7. Literature review and discussion

Somatic *EGFR* mutations are relatively common among patients with lung cancer who have been light smokers, with an incidence of between 10 and 40 % depending on patient ethnicity [11]. Constitutional pathogenic variants in cancer predisposition genes in patients with lung cancer have been reported, although whether these are incidental or contributory has not been clarified in all cases. In a series involving 7668 patients with lung cancer, 5.8 % were found to carry at least one (likely) pathogenic variant in a cancer susceptibility gene, but this reported figure included carriers of recessive traits and low penetrance common founder variants [12]. *EGFR* variants were identified in 12 patients in this series, but it should be noted that reporting was restricted to only four common variants [12]. Several genes have been reported as candidate lung cancer susceptibility genes (*ATM, BRCA2, STK11*), but data supporting gene-disease association is strongest for *TP53* [13] and *EGFR* [14].

The R776H mutation has been previously reported in lung tumour tissue, usually alongside additional pathogenic *EGFR* somatic variants [15]. This variant has also been reported as a constitutional event in other families in the literature. Van Noesel et al (2013) reported the case of a family with squamous cell carcinoma and the R776H constitutional mutation with secondary somatic variants occurring in addition [15]. Of note, the somatic variants were also at G719.

Li et al (2023) described a 45-year-old patient with synchronous breast and lung cancer [16]. The lung cancer carried an *EGFR* L861Q and R776H mutation; the patient was treated with gefitinib. On disease progression, a liquid biopsy found the *EGFR* R776H mutation with variant allele frequency (VAF) 49.1 %, consistent with germline origin. The other identified *EGFR* mutations were present at low VAFs (<3%). The patient's older sisters had died from lung cancer at age 53 and 40 years, and a younger sister was diagnosed with lung cancer at age 44. All three siblings were also carriers for the *EGFR* R776H germline variant. There was one sister who had not developed lung cancer and did not carry the familial germline variant.

Guo et al (2021) describe a patient with early-stage adenocarcinoma demonstrating *EGFR* G719A and germline R766H mutation [17]. The patient's mother had also been previously treated for lung cancer but did not carry the germline mutation on testing. However, the teenage son of the patient was found to have inherited the familial variant, and CT scan showed multiple ground glass nodules in both lungs. He is under regular CT surveillance.

These cases are summarised in Table 1 below. These families demonstrate several similarities to our cases. Importantly is the observation of co-occurrence with germline R776H and second somatic events; also particularly noteworthy is the co-occurrence of variants at G719.

In the Catalogue of Somatic Mutations in Cancer of the Wellcome Trust Sanger Institute (COSMIC), the R776H somatic mutation has been reported in nine cases of NSCLC [18]. In these cases, there was also an additional *EGFR* mutation: usually either the more common G719A or L858R mutations. The germline origin of the R776H mutation was not assessed in any of these cases so these patients may also carry the mutation in the germline. If this was the case, then this germline variant could have a frequency of 0.4 % among patients with *EGFR* mutation NSCLC [15].

In general, it seems that the *EGFR* pathogenic variant identified in the germline of our patients also occurs as a somatic event, often in addition to other somatic *EGFR* variants. Initially, for our patients the germline variant was not found during somatic testing, as bioinformatic germline subtraction filtered it out of the reporting pipeline. We have rechecked DNA from the previous tissue samples for all three of the sisters on a multigene panel in 2023 and confirmed the presence of the R776H variant in tumour-derived DNA from samples from all 3 patients, with high VAF (>40 %) measurable in 2 of the 3 cases, consistent with the germline origin of the variant.

Oxnard et al published the results of their Investigating HEreditary RIsk from T790M (INHERIT) study (2023) [10]. The aim of the study was to determine the prevalence of germline *EGFR* T790M in patients with T790M variants identified during tumour-based testing [10]. As with germline *EGFR* R776H mutations, germline T790M mutations are rare. However out of 46 patients with lung cancer with somatic *EGFR* T790M at diagnosis, 24 (52 %) carried a germline pathogenic variant. Another 22 patients were found to carry a different germline *EGFR* mutation (other than T790M). For all variants, penetrance was variable both within and among kindreds. They noted that penetrance was high in the one family carrying germline *EGFR* R776H, which fits with our case family.

They also found that of the 37 participants with lung cancer and a germline PV, where tumour-based *EGFR* genotyping was undertaken, an EGFR co-mutation was detected in 35 (95 %). The spectrum of the 36 somatic *EGFR* mutations seen in 35 germline carriers was atypical, again similar to the other reported cases.

The case reports reflect a wide range of ethnicities and ages although

Table 1
Literature Review of Lung Cancer Patients with Germline EGFR R776H Mutations.

Family	Author	Year	Age at dx	Gender	Ethnicity	Smokinghistory	Histology	Somatic Mutation	Treatment	Survival
1	Centeno [33]	2011	47	M	European	Yes	Undifferentiated Adenocarcinoma	R776H L858R	Surgery	12 m
2	Van Noesel [15]	2013	57	F	American	No	Squamous cell	R776H G719A	CRT	17 m
			36	F	American	No	Squamous cell	R776H G719S	Surgery, erlotinib	>12 m
3	Kai Su [32]	2018	52	F	Eastern Asian	No	Adenocarcinoma	None	Surgery	Unkn
4	Guo [17]	2021	42	F	Eastern Asian	No	Adenocarcinoma	G719A	Surgery	>12 m
			17	M	Eastern Asian	No	N/A	Unkn	Surveillance	N/A
5	Sovich [9]	2022	50	F	American	No	Adenocarcinoma	R776H L861R	Osimertinib	>6m
6	Li [16]	2023	45	F	Eastern Asian	No	Adenocarcinoma	R776H L861Q	Gefitinib, Osimertinib	42 m
7	*Present case*	2023	37	F	White British	Yes	Adenocarcinoma	G719X	Afatinib	48 m
			41	F	White British	Yes	Adenocarcinoma	G719XL861Q	Afatinib	>5 yrs
			43	F	White British	Yes	Adenocarcinoma	G719XL861Q, L858R	Afatinib	>5 yrs

the majority are female. The average age at diagnosis is 42.5 years. Most of these cases are adenocarcinoma and were able to be treated with surgery although tyrosine kinase inhibitors (TKI) have also been used with good effect [16]. The average OS is 29 months although some data is missing. Our cases can now be added to this literature.

The daughter of our Patient 3 is in her 20s and has been diagnosed with and radically treated for follicular thyroid cancer. Kim et al (2017) reported an association between thyroid cancer and family history of thyroid cancer with female patients with *EGFR* mutant NSCLC [19].

There is a lack of evidence base and knowledge around the appropriate management and follow up of patients with germline mutations or who appear to be at high risk of lung cancer due to their family history, especially if they are young.

Germline genetic testing in patients with lung cancer is currently not routinely recommended outside of research studies. Clearly, early diagnosis, optimal management and ultimately prevention of hereditary lung cancers in patients with known variants that increase the risk of lung cancer will require more information from research studies. We await reports from the ongoing INHERIT-EGFR study among others [10].

7.1. Management of uncommon EGFR mutations

There are treatment challenges associated with familial lung cancer and rare *EGFR* mutations. It has been reported that patients with rare *EGFR* mutations do not respond as well to first generation TKIs although evidence is relatively limited [20]. Previous case series have reported response rates of 14–15.3 % to first generation EGFR-TKIs for these *EGFR* mutations and median progression free survival (mPFS) of 5.98–11.6 months and a median overall survival (mOS) of 19.8–25.2 months [21,22].

G719X mutations have also been reported as responsive to the second-generation EGFR-TKI afatanib and neratinib. One study showed an overall response rate of 77.8 % with mPFS of 13.8 months, mOS of 26.9 months [23] similar that for the classic EGFR mutations [24].

Huang et al (2021) report a case of long-term survival in a patient with adenocarcinoma harbouring an *EGFR* G719A mutation treated with afatanib for 11 years [25]. The use of afatinib was based on the data and availability of tyrosine kinase inhibitors in 2017. Osimertinib was not approved as first line treatment until 2018 [26].

In our reported family of 3 cases it is more complicated due to the presence of compound mutations. However, the mPFS for our patients has on average, been significantly longer than other reported cases.

7.2. Smoking and environmental risk factors

There is significant over representation of never or minimal smokers among lung cancer cases with an *EGFR* mutation [22]. Worldwide, the most significant risk factor for the development of lung cancer is tobacco smoke and it is likely that close to 90 % of all cases are directly attributable to smoking cigarettes [1]. Lung cancers associated with either sporadic somatic or germline *EGFR* variants seem to link to never-smoking status, female gender and adenocarcinoma histology [11].

Other environmental factors are also known to increase the risk of lung cancer [2,27], however in this case the patients' jobs are office-based with no industrial involvement. Radon is a colourless, odourless gas which is produced by the breakdown of uranium in soil and rock [28]. Levels vary widely and depend on the type of underlying soil. Our case study family are from South London where the levels of radon are among the lowest in the country [29].

Air pollution, for example from burning fossil fuels, biomass, wildfires are also known to be carcinogenic to humans regardless of smoking history [30]. It is possible that air pollution in the presence of pre-existing mutations which predispose to the development of lung cancer could have contributed. Hill et al (2023) suggest that air pollution in the form of particulate matter (PM) could stimulate the proliferation of mutated lung cells through an inflammatory process which leads to tumour formation [31]. Air pollution in the Greater London area which is where our patients grew up has been steadily improving over the past 40 years [32]. However, the levels of PM2.5 which has been identified as particularly linked in the Hill paper are above the WHO recommended level of < 5 μg m^{-3} annually. The average urban background PM2.5 in Greater London in 2015–2019 was 10.1 μg m^{-3}, according to the UK Government [32]. It may be relevant but unquantifiable in this case.

8. Conclusion

This Caucasian family demonstrates the presence of a previously reported germline *EGFR* mutation in two generations with three cases of Stage IV adenocarcinoma with a light smoking history. Their tumours demonstrated additional somatic variants in addition to the germline variant, indicating that second hits may be a necessary oncogenic mechanism, potentially due to the smoking history. The reason for predilection at G719 has yet to be elucidated.

All three patients have been treated with afatanib, adding to the literature suggesting this may be a suitable option for treatment of adenocarcinoma of the lung with uncommon *EGFR* mutations.

We agree with Oxnard et al and wonder if our patients may have a multifocal, polyclonal malignant process rather than a single metastatic lung cancer process [10], since two of the sisters had several lung nodules at diagnosis. This may be in addition to the specific somatic *EGFR* mutations seen within the tumours.

These cases highlight the importance of a thorough and comprehensive family history as part of lung cancer management which may alert the clinician to the possibility of a genetic component. Benusiglio et al (2022) suggest this is especially important in patients who are under 50 years, have a somatic *EGFR* activating mutation or a family history in a 1st or 2nd degree relative under the age of 56 years [33]. It has been suggested that meeting these criteria should warrant referral to a clinical geneticist for further assessment [34].

At present, classification of constitutional variants in cancer susceptibility genes are based on guidance designed to determine pathogenicity of highly penetrant Mendelian traits [35,36]. For those rare variants associated with incomplete penetrance, gathering sufficient evidence points to achieve a classification of (likely) pathogenic is difficult. At present, the R776H variant has been reported by the lab as a variant of uncertain significance, although evidence from this and other reported families suggests it is likely to be at least contributory to disease risk and may be more appropriately described as a risk allele associated with incomplete (and/or uncertain) penetrance.

Currently, constitutional genetic testing is recommended where there is a reasonable *a priori* probability of identifying at least a moderately penetrant germline pathogenic variant. Testing for, and reporting of, low penetrance risk alleles, or variants for which penetrance estimates have not been defined are not recommended routinely. Decisions as to whether testing of "new" cancer susceptibility genes should be considered is guided by ACCE framework (Analytical validity, Clinical validity, Clinical utility, and Ethical, legal, and social issues).

Testing is usually recommended if clinical management of a carrier will be changed. At present, how (if at all) carriers of variants in *EGFR* should be screened, the age at which screening should commence, and whether surveillance impacts survival is unclear. Further research is needed to determine this, including collation of cases where constitutional variants in *EGFR* are confirmed or suspected.

Methodological approaches to identify rare *EGFR* mutations in diagnostic specimens in routine clinical care are generally allele-specific approaches based on PCR or next generation sequencing (NGS) approaches [37]. Allele-specific approaches will only identify mutations whose presence or absence is being evaluated, and hence are most likely to not identify rare, very rare, or novel pathogenic *EGFR* variants. By contrast, NGS will sequence whole regions and is most likely to identify these *EGFR* variants, assuming they lie with the region sequenced, since

EGFR gene coverage can vary between platforms [37]. Both approaches can be implemented on tumour tissue or on plasma.

Molecular testing platforms using blood cell free (cf) DNA are increasingly used to provide detection of *EGFR* mutations at a faster speed than tissue biopsy and are also a less invasive option [38]. Large scale studies of liquid biopsy technologies are under investigation for their role in the lung cancer diagnostic pathway [38]. This may be particularly helpful when tissue results are negative or inconclusive. However, we feel that cfDNA technology is unlikely to change the criteria for germline testing or have altered the outcome in this case.

In many countries, population screening projects for lung cancer with low dose CT scans is being offered to patients aged between 55 and 74 with a history of smoking that meets a certain threshold [36]. This will identify patients with a high risk of lung cancer based on environmental exposure, but it is not yet known how this might impact our approach to screening carriers of possible germline variants and more research will be needed here too.

Reporting families with lung cancer, and an identified germline *EGFR* variant, is necessary, and will contribute to changes in future guidelines for germline testing.

9. Statement of consent

The authors have obtained permission from the patients to publish the information in this case report of the family.

CRediT authorship contribution statement

L. Gabriel: Writing – original draft, Project administration, Investigation. **T. McVeigh:** Writing – review & editing, Methodology, Data curation. **S. Macmahon:** Writing – review & editing, Visualization, Investigation. **Z. Avila:** Resources, Investigation. **L. Donovan:** Investigation, Resources. **I. Hunt:** Investigation. **A. Draper:** Investigation. **A. Minchom:** Supervision, Writing – review & editing. **S. Popat:** Methodology, Supervision, Writing – review & editing. **M. Davidson:** Supervision, Writing – review & editing. **J. Bhosle:** Writing – review & editing. **C. Milner Watts:** . **M. Hubank:** Resources, Investigation. **L. Yuan:** Investigation, Resources. **MER O'Brien:** Conceptualization, Data curation, Investigation, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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