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Review

Epidermal growth factor receptor mutation and diverse tumors: Case report and concise literature review

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ABSTRACT

We document an EGFR mutation in a patient with papillary renal cell cancer with a history of multiple therapies, including interferon-alfa, interleukin-2, 5-fluorouracil, and interferon-alfa together with 13-cis-retinoic acid, to which floxuridine was later added, and thalidomide maintenance therapy for six years. We provide a succinct review of the PubMed-derived literature on *EGFR* mutations in diverse tumors, which indicates that a subset of patients with various tumor types may harbor *EGFR* mutations. A 32-year old woman with sporadic, metastatic papillary renal cancer was found to harbor an EGFR kinase domain mutation in addition to the *MET* kinase mutation typically found in this disease. Since lung cancer patients with EGFR mutations often respond well to EGFR inhibitor therapy and *EGFR* mutations occur in a variety of tumors, it should be worthwhile to assess EGFR status prospectively in other tumors and study the results of treatment with EGFR inhibitors in these patients.

1. Background

Papillary histology in renal cell carcinoma is seen in about 15–20% of kidney tumors. There are two forms, hereditary and sporadic. The former is inherited in an autosomal dominant fashion and is associated with germline mutations in the tyrosine kinase domain of the *MET* gene at 7q31 (Schmidt et al., 1997) In sporadic papillary renal tumors, activating *MET* mutations are discerned in the tumor tissue (but are not germline) of about 13% of patients (Lubensky et al., 1999). Understanding the mutation status of tumors is important because of recent discoveries demonstrating significant salutary effects for drugs targeting specific mutations. For this reason, small molecule inhibitors of MET kinase are under development, and show early signs of clinical efficacy.

A movement towards personalized therapy is occurring in cancer because of increasing evidence that targeted agents can induce responses with only minimal toxicity in patients whose tumors harbor the appropriate aberrant target. For instance, following treatment with epidermal growth factor receptor (EGFR) inhibitors, clinically important responses have been observed in patients with lung cancer bearing a mutation of the *EGFR* gene (Lynch et al., 2004). Overall, *EGFR* mutations are found in about 10% of patients with non-small cell lung cancer (Lynch et al., 2004; Tibes et al., 2005). They have also been reported in other tumors, albeit uncommonly.

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Abbreviations: EGFR, Epidermal growth factor receptor.

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In this report, we document an *EGFR* mutation in a patient with sporadic papillary renal cell cancer and a *MET* mutation. We also provide a concise review of the literature pertaining to *EGFR* mutations in diverse tumor types beyond their recognized role in lung cancers. The case report was obtained by reviewing the patient medical records. Review of the literature was performed via a PubMed search. The report was compiled in accordance with our IRB guidelines.

2. Case presentation

A 32-year old woman was diagnosed with metastatic papillary renal cell carcinoma, for which she underwent left nephrectomy followed by multiple therapies that included interferon-alfa, interleukin-2, 5-fluorouracil, and interferon-alfa together with 13-cis-retinoic acid, to which floxuridine was later added. In addition, the patient was treated with thalidomide maintenance therapy for a total of six years.

At her initial visit to our clinic, the patient looked well and was asymptomatic and her physical examination was normal. Her work-up, including complete blood count with differential, and renal and liver function tests, was within normal limits. Computer tomography of her chest, abdomen and pelvis revealed metastatic disease bilaterally in the lungs. Genetic analysis of the tissue sample from her lung revealed *MET* and *EGFR* mutations. Pathology was reviewed at M. D. Anderson Cancer Center by a pathologist specializing in urologic cancer, who concurred with the diagnosis of papillary renal cell cancer.

Mutation scanning of the *EGFR* and *MET* genes was undertaken. Genomic DNA was extracted from the patient's lung biopsy specimen; exons 18–21 (for EGFR kinase domain) and 14–18 (for MET kinase domain) were amplified by polymerase chain reaction using thermostable proofreading enzyme optimase polymerase. The products were then scanned for mutations by WAVE® denaturing high-performance liquid chromatography and SURVEYOR® nuclease heteroduplex analysis according to the following methods available at (*Transgenomic Labs, Omaha, NE*). Mutations were confirmed by double-stranded DNA sequencing. Methods for mutation analysis are outlined at http://www.transgenomic.com/lib/ug/482516.pdf.

A single mutation was identified at codon 802 (exon 20) of the EGFR tyrosine kinase domain, predicting an amino acid change from valine to isoleucine. The mutation load in the specimen was calculated to be 10–20%.

Two mutations were identified at codons 969 and 991 of the MET tyrosine kinase domain, predicting amino acid changes from valine to isoleucine and from proline to serine, respectively. There was no mutation in the peripheral blood lymphocytes, indicating that the *MET* mutation was not somatic.

The patient was offered treatment with an experimental MET inhibitor or with an EGFR inhibitor at M.D. Anderson Cancer Center. The patient declined treatment at the center and returned home.

Table 1 – EGFR aberrations and cancer: overview.

Disease	No of patients with *EGFR* mutation total (%)	*EGFR* mutation information	Comment	Reference
Ovarian Cancer	1/25 (4%)	Exon 19 deletion	Patient with mutation was only one to achieve a partial remission on the EGFR inhibitor gefitinib	(Schilder et al., 2005)
Squamous cell cancer of the head and neck	3/41 (7.3%)	Deletion in Exon 19		(Lee et al., 2005)
Cholangiocarcinoma	3/22 (13.6%)	Deletion in Exon 19		(Gwak et al., 2005)
Prostate Cancer	4/89 (4.5%)	Missense mutations in exons 19, 20 and 21		(Douglas et al., 2006)
Colorectal cancer	4/33 (12%)	Mutations in exons 19 (codon 749) or exon 20 (codons 762 and 767)		(Nagahara et al., 2005)
Esophageal	2/17 (11.7%)	Exon 19 deletion and exon 21 L858R mutation		(Kwak et al., 2006)
Barrett's esophagus	3/21 (14.2%)	Deletion in exon 19 (N=2) and exon 20 mutation in T790M	T790M is drug resistant	(Kwak et al., 2006)
Pancreatic cancer	2/55 (3.6%)	Deletion in exon 19	Disease stabilization with erlotinib and capecitabine	(Kwak et al., 2006)
Non-small cell lung cancer	68/278 (24%)	Most commonly exon 19 deletions, exon 21 point mutation L858R	Associated with no prior smoking, prolonged survival and response to EGFR inhibitors	(Sequist et al., 2007)
Non-small cell lung cancer	38/98 (38.8%)	Most commonly exon 19 deletions, exon 21 point mutaion L858R	Japanese population.Associated with no prior smoking, prolonged survival and response to EGFR inhibitors	(Ichihara et al., 2007)

3. Discussion

It is well established that tumors are often driven by aberrant pathways, and elucidating these abnormalities is important for them to become targets for therapy (Tibes et al., 2005). For example, remarkable responses have been seen in patients with gastrointestinal stromal tumors harboring activating mutations in KIT kinase when treated with the KIT kinase inhibitor imatinib (Van Oosterom et al., 2001). Similarly, EGFR inhibitors are particularly effective in patients with lung cancer who bear an activating *EGFR* mutation (Lynch et al., 2004). *EGFR* mutations are rare in other tumors, but have been described in ovarian cancer (4.0% of patients) (Schilder et al., 2005), squamous cell carcinoma of the head and neck (7.3% of patients) (Lee et al., 2005) cholangiocarcinoma (13.6% of patients) (Gwak et al., 2005), prostate cancer (4.5% of patients) (Douglas et al., 2006), colorectal cancer (12% of patients) (Kwak et al., 2006), esophageal cancer (11.7% of patients) (Nagahara et al., 2005), Barrett's esophagus (14.2% of patients) (Kwak et al., 2006), and pancreatic cancer (3.6% of patients) (Kwak et al., 2006) (Table 1). Of interest, EGFR overexpression by immunohistochemistry correlates with EGFR amplification but not necessarily with *EGFR* mutation (Chitale et al., 2008). Therefore, mutation analysis is necessary and immunhistochemistry cannot be used as a surrogate. Although correlation between response to EGFR inhibitors and the presence of mutation has rarely been examined in non-lung cancer tumors, in anecdotal instances where such a correlation was analyzed, response or disease stabilization was noted (Lee et al., 2005; Kwak et al., 2006). Indeed, Schilder et al. (2005) observed a single partial response in a study of gefitinib in ovarian cancer in the one individual who had an activating *EGFR* mutation in that study. Similarly, the two patients with pancreatic cancer and an *EGFR* mutation had prolonged disease stabilization in response to a treatment regimen of erlotinib and capecitabine, suggesting the possibility that they had a more treatable form of this malignancy (Kwak et al., 2006).

EGFR mutations such as found in the patient reported here are not well documented in the literature. Of interest, Rowinsky et al. (2004) observed three major responses (3.4%) (complete response; ($N = 1$): and partial responses ($N = 2$) among 88 patients with metastatic renal cancer treated with a monoclonal antibody to EGFR. Similarly, a subset of patients with head and neck cancer and colorectal cancer respond to molecules that target the EGF receptor. Table 1 provides an overview of EGFR aberrations in different cancers.

4. Conclusions

A movement towards personalized therapy is occurring in cancer because of mounting evidence that targeted agents can often induce responses with only minimal toxicity in patients whose tumors harbor the appropriate aberrant target. Even so, there is a paucity of literature on EGFR status in non-lung tumors, and no prospective study has been performed to analyze EGFR-mutation-positive non-lung tumors for their responsiveness to EGFR inhibitors. The data from the patient reported here, together with the emerging literature reviewed, suggests that it may be worthwhile to analyze tumor DNA from patients with renal cell and other cancers for *EGFR* mutations, and to determine if the subset of patients with mutations respond to EGFR-targeting drugs.

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