CASE REPORT

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Identification of FGFR3-TACC3 gene fusion in metastatic gastric cancer

Youjin Kim[1], Seung Tae Kim[1], Jeeyun Lee[1], Won Ki Kang[1], Kyoung-Mee Kim[2], Se Hoon Park[1]

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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Corresponding author:
Se Hoon Park
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-1767
E-mail: sh1767.park@samsung.com

ABSTRACT

In preclinical cancer models, fibroblast growth factor receptor (FGFR) gene aberration has been known to be associated with increased tumor cell proliferation and survival in several cancer types. Oncogenic fusions consisting of FGFR3 and transforming acid coiled coil 3 (TACC3) had been identified as potential therapeutic target. We report on a gastric cancer patient with liver metastases who harbored FGFR3-TACC3 fusion which is extremely rare in gastrointestinal cancer. Herein, we report a case presentation with literature review of FGFR3-TACC3 fusion.

Keywords: FGFR3-TACC3; Metastatic gastric cancer

INTRODUCTION

Gastric cancer (GC) is the second most common cause of cancer-related deaths worldwide, and the prognosis of advanced gastric cancer is still poor [1,2]. The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) system consists of 18 ligands (FGFs) and four receptors (FGFR1-4) [3,4]. Upon ligand binding FGFRs activate several signaling cascades, particularly phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinases (MAPK)/extracellular-signal-regulated kinase (ERK) [5]. In turn, this leads to regulation of diverse cellular functions which play a pivotal role not only in physiological homeostasis but also in carcinogenesis, e.g. proliferation, motility, angiogenesis, anti-apoptosis and drug resistance [3,6]. More recently, FGFR fusion proteins have been increasingly detected in various human cancers, and transforming acid coiled coil 3 (TACC3) gene has been identified as an important partner of these FGFR fusions and was known to force dimerization and consequently activation of FGFR3 kinase activity in several solid tumors [7,8]. The contribution of such fusions to cancers of the upper digestive tract has remained largely unknown, but was detected in esophageal squamous cell carcinoma, recently [9,10]. Here we report a case of metastatic GC harboring an activating FGFR3-TACC3 mutation for the first time.

CASE REPORT

In August 2010, a 52-year-old man was referred to our hospital for treatment of gastric cancer which was identified during annual endoscopic examination as part of national cancer screening program in Korea. The initial computed tomography (CT) scan at diagnosis demonstrated wall thickening in the lesser curvature of the lower body without any evidence for distant metastasis. He received curative subtotal gastrectomy, Billroth I anastomosis, D2 dissection and the

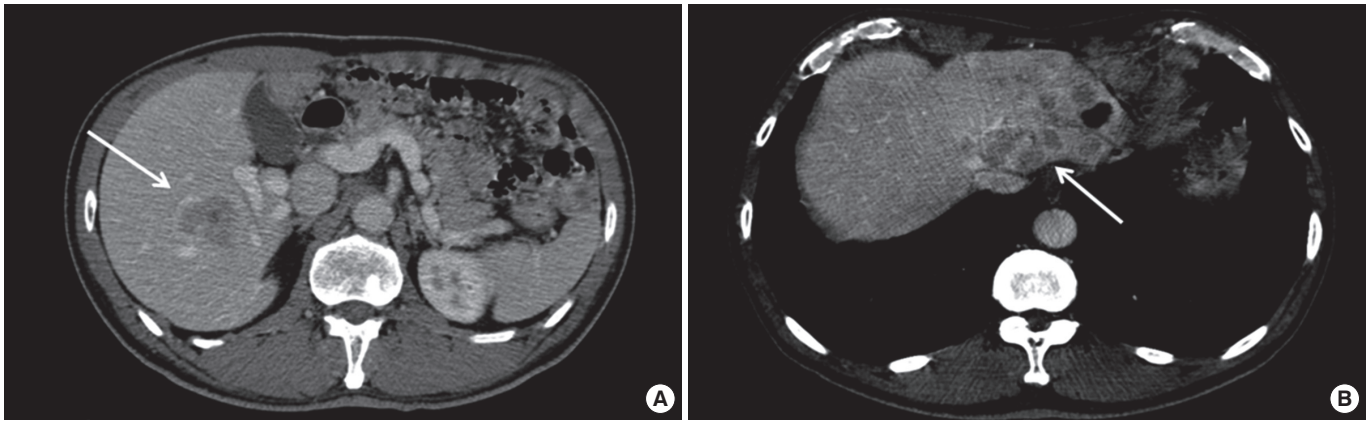

Fig. 1. Computed tomography of the abdomen after 15 months since surgery. It showed multiple hepatic metastases, medium-sized and small nodules in the (A) right (arrow) and (B) left (arrow) hepatic lobes.

Table 1. Cross-sectional studies and case series reporting positive FGFR-TACC3 fusions

Study	Tumor type	No. of case analyzed	No. of case harboring	Positive rate (%)
Parker et al. (2013) [14]	Glioblastoma	48	4	8.33
Bao et al. (2014) [15]	Glioblastoma	59	3	5.08
Singh et al. (2012) [16]	Glioblastoma	97	2	2.06
Williams et al. (2013) [17]	Bladder carcinoma	32	2	6.25
Cancer Genome Atlas Research Network (2014) [18]	Bladder carcinoma	114	3	2.60
Helsten et al. (2016) [19]	Cervical cancer	48	2	4.17
Xiang et al. (2015) [20]	Cervical cancer	285	11	3.86
Helsten et al. (2016) [19]	Urothelial carcinoma	126	4	3.17
Di Stefano et al. (2015) [21]	Gliomas	795	20	2.51
Yuan et al. (2014) [22]	Nasopharyngeal carcinoma	130	3	2.30
Helsten et al. (2016) [19]	Gallbladder carcinoma	47	1	2.13
Majewski et al. (2013) [23]	NSCLC (SqCC)	95	2	2.11
Kim et al. (2014) [24]	NSCLC (SqCC)	104	2	1.92
Capelletti et al. (2014) [7]	NSCLC (ADC)	576	3	0.52
Helsten et al. (2016) [19]	NSCLC (subtype not specified)	675	1	0.15
Yuan et al. (2014) [22]	Esophagus cancer (SqCC)	48	1	2.10
Helsten et al. (2016) [19]	Endometrial carcinoma	80	1	1.25
Helsten et al. (2016) [19]	Renal cell carcinoma	87	1	1.15
Helsten et al. (2016) [19]	Pancreatic exocrine tumor	172	1	0.58
Helsten et al. (2016) [19]	Carcinoma of unknown primary	267	1	0.37

FGFR-TACC3, fibroblast growth factor receptors-transforming acid coiled coil 3; NSCLC, non-small cell lung cancer; SqCC, squamaous cell carcinoma; ADC, adenocarcinoma.

pathologic examination revealed a moderately-differentiated adenocarcinoma, pT3N0M0, stage IIA (erbb2 negative). As postoperative adjuvant treatment, the patient completed 8 cycles of TS-1 chemotherapy given the pathologic stage. During scheduled surveillance for recurrence, the patient developed multiple liver metastases after 15 months postsurgery (Fig. 1). Liver biopsy was performed and the pathology revealed metastasized gastric adenocarcinoma. He received first-line capecitabine/oxaliplatin (oxaliplatin 130 mg/m^2+ capecitabine 1,000 mg/m^2 by mouth twice a day, day 1 to 14) every 21 days, and achieved partial response for 5 months. Follow-up CT scan still showed 1.1 cm metastatic lesion in S6 which was further ablated by CT-guided percutaneous radiofrequency ablation (RFA). The patient received ramucirumab/paclitaxel with complete remission after RFA until he developed another liver metastases. We identified FGFR3-TACC3 fusion in his tumor using next-generation sequencing (NGS) platform that we routinely use in the clinic (Oncomine™ Comprehensive Assay v3, www.thermofisher.com).

DISCUSSION

Recent advances in sequencing technologies have led to an increase in the discovery of novel and therapeutically actionable genomic alterations in a broad range of cancers. Comprehensive clinical sequencing programs for cancer patients have been initiated at a variety of medical centers including

Table 2. Summary of FGFR inhibitors currently investigated in clinical trials

Inhibitor (manufacturers)	Cancer type	Identification of Clinicaltrials. gov	Phase	Estimated enrollment (n)
Dovitinib (Novartis)	FGFR3-mutated or -overexpressed urothelial cancer	NCT01732107	II	50
	Metastatic renal cell cancer (Dovitinib versus sorafenib)	NCT01223027	III	564
Ponatinib (ARIAD Pharmaceuticals)	FGFR genetically aberrant advanced-stage cancers	NCT02272998	II	45
Lucitanib (Clovis Oncology)	Any FGF-related aberration in advanced or metastatic lung cancer	NCT02109016	II	18
AZD4547 (AstraZeneca)	FGFR genetically aberrant NSCLC	NCT02664935	II	620
	FGFR genetically aberrant NSCLC	NCT02117167	II	650
NVP-BGJ398 (Novartis)	FGFR1–3 genetically aberrant solid tumors, FGFR1-amplified squamous cell lung cancer, FGFR3-mutated or fused bladder cancer	NCT01004224	I	208
	FGFR genetically aberrant advanced solid tumors in an Asian population	NCT01697605	I	22
	FGFR genetically aberrant advanced solid tumors with PIK3CA mutations	NCT01928459	I	62
	Glioma subtypes with FGFR1-TACC1 fusion, FGFR3-TACC3 fusion, activating mutation in FGFR1–3	NCT01975701	II	24
	FGFR genetically aberrant solid or hematological cancers	NCT02160041	II	90
	FGFR genetically aberrant advanced or metastatic cholangiocarcinoma	NCT02150967	II	120
JNJ-42756493 (Janssen)	FGFR genetically aberrant advanced urothelial cancer	NCT02365597	II	210
	Asian participants with NSCLC, gastric cancer, urothelial cancer, esophageal cancer, cholangiocarcinoma	NCT02699606	II	75
LY2874455 (Lilly)	Advanced-stage cancer	NCT01212107	I	94
TAS120 (Taiho Oncology)	FGFR genetically aberrant advanced solid tumors or multiple myeloma	NCT02052778	I	835
Debio-1347 (Debiopharm International)	FGFR1–3 genetically aberrant solid tumors I	NCT01948297	I	112
FP-1039 (GlaxoSmithKline)	FGFR genetically aberrant solid malignancies in combination with paclitaxel and carboplatin or docetaxel	NCT01868022	I	120
	Advanced solid tumors I	NCT01363024	I	24

FGFR-TACC3, fibroblast growth factor receptors-transforming acid coiled coil 3; NSCLC, non-small cell lung cancer; PIK3CA, phosphoinositide-3-kinase, catalytic, alpha polypeptide.

our center [11]. Recently, FGFR3-TACC3 gene fusion has been identified in several cancers including glioblastoma, lung cancer, bladder cancer, oral cancer, head and neck squamous cell carcinoma, gallbladder cancer, and cervical cancer. We summarized the incidence of FGFR3-TACC3 rearrangements in various tumor types in Table 1 that had been reported in the literature [7,12-24]. To the best of our knowledge, FGFR3-TACC3 fusions have not previously been described in GC.

FGFR3–TACC3 fusion proteins appear to localize to spindle poles and cause disruption of chromosome segregation and aneuploidy by a mechanism dependent on FGFR tyrosine kinase activity [25]. The tumor-initiating activity of the FGFR3-TACC3 fusion protein suggests that it has growth-promoting signaling functions that complement the loss of mitotic fidelity and aneuploidy to induce full-blown tumorigenesis. The clinical relevance of FGFR3-TACC3 has been underscored by preliminary results from clinical studies and case reports of tumor responses to the treatment with FGFR inhibitors. For instance, the phase I trial with FGFR inhibitor JNJ-42756493 including 65 patients with advanced solid tumors included 4 patients with FGFR3-TACC3 translocation [26]. We outlined the evidence from early phase clinical trials support that FGFR aberrations can represent targetable events and several clinical trials of FGFR inhibitors, including with BGJ398 (NCT01928459, NCT 01975701, NCT01697605, and NCT01004224), are currently under clinical development in Table 2 [13].

This report is the first to identify FGFR3-TACC3 fusion proteins in gastric cancer, and it provides proof of concept that treating with an FGFR inhibitor can result in clinical benefit in metastatic GC carrying FGFR3-TACC3 translocation in agreement with results observed in other malignancies. In addition, our findings suggest the importance of a comprehensive genomic profiling approach able to detect all classes of genomic alterations including uncommon gene fusions to reveal potentially targetable somatic alterations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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