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CASE REPORT

FGFR2-TSC22D1, a novel *FGFR2* fusion gene identified in a patient with colorectal cancer: A case report

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Author contributions: Fan CG performed the conception and design of the study; Kao XM and Zhu X performed the acquisition of clinical data; Zhang JL and Chen SQ performed the analysis and interpretation of the data; Fan CG and Kao XM performed the manuscript drafting and revision; all authors performed the final approval of the manuscript.

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Abstract

BACKGROUND

The FGFR signaling pathway is activated in multiple tumor types through gene amplifications, single base substitutions, or gene fusions. Novel *FGFR* gene fusions may represent candidate targets for the development of tyrosine kinase inhibitors.

CASE SUMMARY

Herein, we report a patient with colorectal cancer (CRC) harboring a novel *FGFR2* fusion gene. A 59-year-old man felt discomfort in his right upper abdomen with loss of appetite for 6 mo. An abdominal computed tomography scan revealed the existence of a space-occupying lesion in the ascending colon. The pathological diagnosis was a poorly differentiated adenocarcinoma. Subsequent biopsy specimen was subjected to next-generation sequencing analysis, and a novel *FGFR2-TSC22D1* fusion with complete kinase structure of FGFR2 protein was identified.

CONCLUSION

We report the first case of CRC harboring *FGFR2-TSC22D1,* which enriches the *FGFR2* fusion spectrum. FGFR2 inhibitors might be effective in the later treatment for this patient.

Key Words: *FGFR2-TSC22D1*; Colorectal cancer; Next-generation sequencing; Case report

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Core Tip: A colorectal cancer patient had a novel *FGFR2-TSC22D1* fusion which included exons 1-17 of *FGFR2* and exons 3 of *TSC22D1*. This fusion contains *FGFR2* kinase domain and coil coiled domains encoded by *TSC22D1* exon 3, which might induce oncogenesis. Our case enriches the *FGFR2* fusion spectrum. We believe that these novel findings have important implications in the strategy development of therapy for colorectal cancer.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer-related death worldwide and the 3rd most common cancer in males[1]. In recent years, the burden of CRC is increasing rapidly in China[2]. With the advent of targeted drugs such as epidermal growth factor or vascular endothelial growth factor tyrosine kinase inhibitors (TKIs), the overall survival of CRC increased from the past 8-12 mo to 30 mo nowadays[3-5].

FGFR fusions in solid tumors are caused by chromosomal rearrangements. FGFR families includes FGFR1-4, four highly conserved receptor tyrosine kinases, among which FGFR2 has been proven to be a potential target of FGFR TKI inhibitors. At the same time, in many solid tumors, such as urothelial carcinomas and intrahepatic cholangiogarcinomas, FGFR activating molecular alterations (including *FGFR3* mutations and *FGFR2* fusions) have been found, expanding the options for patients who may benefit from FGFR inhibitors[6]. With the development of next generation sequencing (NGS), some uncommon genomic mutations are detected, such as *FGFR2-PPHLN1*[7], *FGFR2-BICC1*[8], and *FGFR2-CCDC6* fusion mutations[9]. In this case, with the help of NGS detection technology, we found a CRC patient carrying a rare *FGFR2-TSC22D1* fusion gene, which further expanded the *FGFR2* fusion variant spectrum.

CASE PRESENTATION

Chief complaints

A 59-year-old male patient with right upper quadrant pain and discomfort, and no appetite for 6 mo, was referred to our hospital for further treatment.

History of present illness

Six months ago, the patient developed right upper abdominal distension, pain, and discomfort without obvious inducement, accompanied by anorexia. No nausea, vomiting, chills, high fever, palpitation, shortness of breath, or yellow staining of skin and mucous membrane was noted. At a local hospital, colorectal examination revealed an ulcerative mass in the liver flexure of the ascending colon. There was a 0.6 cm × 0.6 cm polyp in the middle of the transverse colon. Pathological report suggested that the ascending colon mass was poorly differentiated adenocarcinoma.

Physical examination

Physical examination revealed that the patient's body temperature was 36.8 °C, heart rate 78 bpm/min, respiratory 16 bpm/min, and blood pressure 122/78 mmHg.

Laboratory examinations

The white cell count was 9.46 × 10^9/L, hemoglobin was 62 g/mL , and platelet count

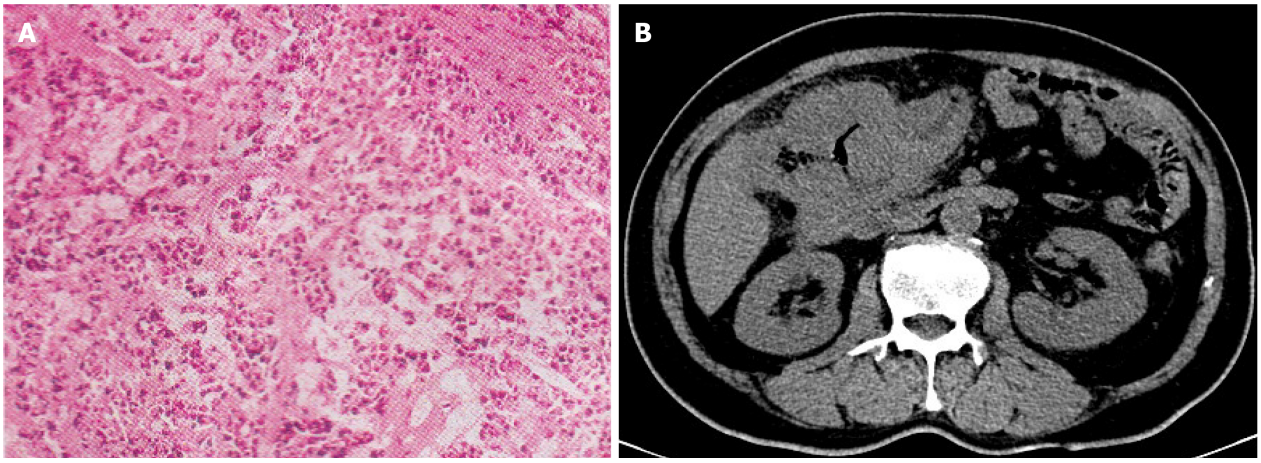

Figure 1 Pathological detection. A: Hematoxylin and eosin staining; B: Abdominal computed tomography showed a tumor lesion in the ascending colon.

was 451 × 10^9/L. Serum tumor markers carcinoembryonic antigen (7.58 ng/mL), carbohydrate antigen (CA)19-9 (21.63 U/mL), CA125 (44.85 U/mL), CA242 (21.57 IU/mL), CA724 (8.38 IU/mL), and CA153 (4.59 IU/mL) were detectable.

The pathological diagnosis under ascending colonoscopy was poorly differentiated adenocarcinoma (cT4N+M0, Figure 1).

The tissue biopsy specimens were then analyzed by NGS and a rare intergenic region between *FGFR2* and *TSC22D1* fusion variation was detected (Figure 2A and B). *TSC22D1* (TSC22 domain family protein 1) gene is a transcription factor belonging to a large family of early response. Dimers of TSC22D1 act as a transcription factor and have tumor suppressor function. The *FGFR2-TSC22D1* fusion gene includes exons 1-17 of *FGFR2* and exons 3 of *TSC22D1*, retaining the complete kinase structure of FGFR2. The ratio of FAM-positivity (*FGFR2* gene) to VIC (internal reference gene) was 0.0048 in droplet digital polymerase chain reaction (ddPCR), indicating weakly *FGFR2* expression (Figure 2C) and proving that *FGFR2* was positive.

Imaging examinations

A computed tomography scan of the abdomen showed the presence of a space-occupying lesion in the liver flexure of the ascending colon.

FINAL DIAGNOSIS

The patient was finally diagnosed as having stage cT4N+M0 CRC and carrying the novel *FGFR2-TSC22D1* fusion gene.

TREATMENT

Based on pathological staging, the patient was given preoperative chemotherapy for tumor down-staging. The regimen is oxaliplatin (200 mg, D1, intravenous drips) plus capecitabine (1500 mg, D1-14, oral). After six cycles of preoperative chemotherapy, the patient underwent radical resection for CRC.

OUTCOME AND FOLLOW-UP

Postoperative pathology showed that no residual cells were found in the duodenal wall, which suggested that a pathological complete response has been achieved.

DISCUSSION

FGFR2 fusions have been identified as a novel oncogenic target for drug development

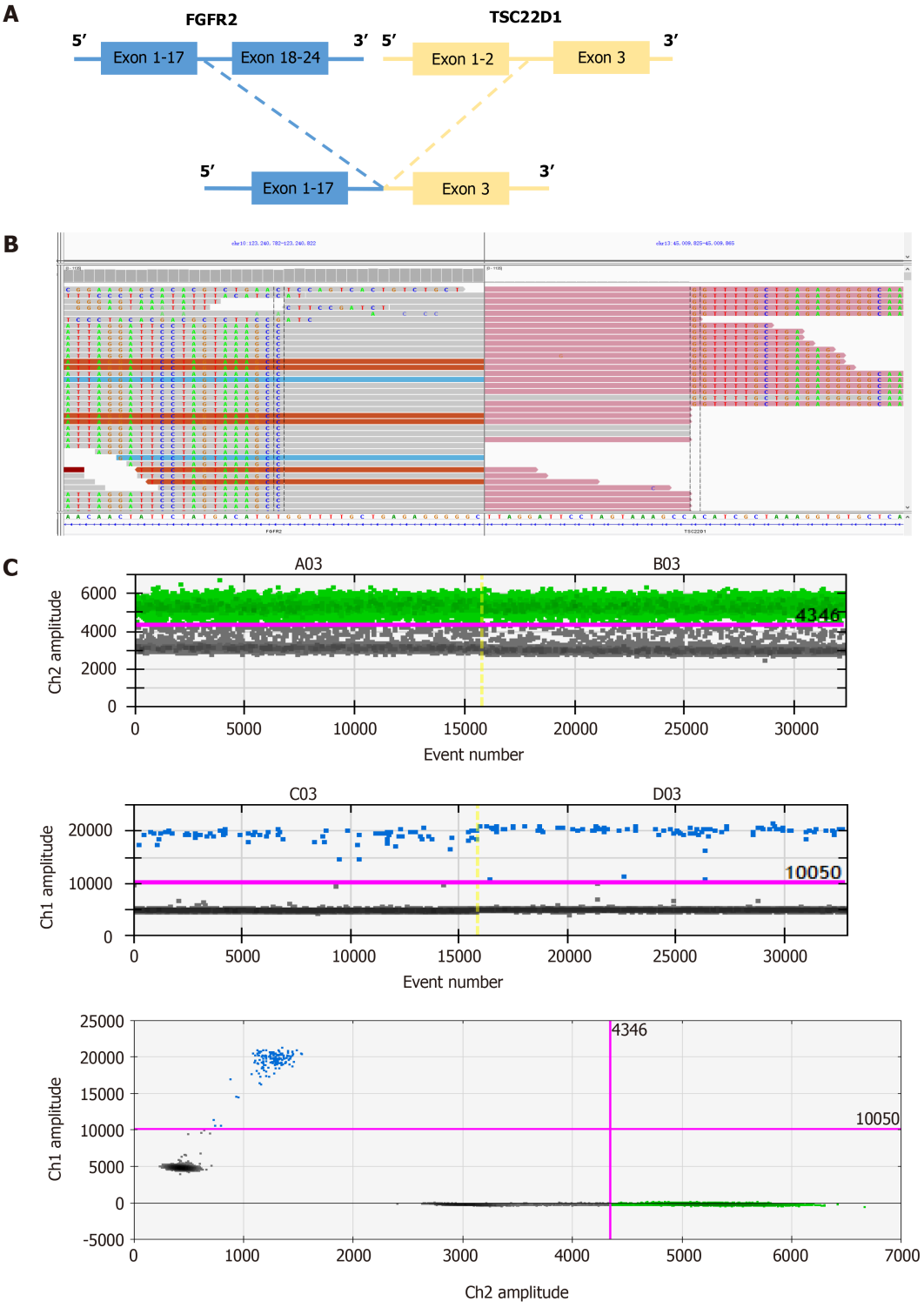

Figure 2 Next-generation sequencing and droplet digital polymerase chain reaction findings for the primary tissue sample. A: A novel intergenic region between *FGFR2* exons 1-17 and *TSC22D1* exon 3 was identified; B: Next-generation sequencing results showing the breakpoint of the *FGFR2-TSC22D1* fusion; C: Droplet digital polymerase chain reaction (ddPCR) amplification charts. Ch1 is FAM Channel (mutant type) and Ch2 is VIC channel (wild type). In these charts, black points represent PCR negative droplets, and blue and green points represent PCR positive droplets in FAM channel and VIC channel, respectively.

in a number of cancers including breast cancer[10] and intrahepatic cholangiocarcinoma[7-9]. Interestingly, a novel *FGFR2* gene fusion was identified in the CRC patient reported in this paper, suggesting that this event may represent a new candidate therapeutic target for which similar strategies could be used in the clinical management.

A comprehensive understanding of *FGFR2* fusion information seems to be necessary. NGS could be used as a supplementary method for *FGFR2* variation for

high-throughput molecular analysis, while detecting gene copy number alterations, fusions, insertions, and deletions simultaneously.

CONCLUSION

In our case, a rare *FGFR2* fusion gene, confirmed by ddPCR, was found, which enriched the *FGFR2* fusion spectrum. FGFR2 inhibitors might be effective in the later treatment for this patient.

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