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Case Report

Detection of Anaplastic Lymphoma Kinase Gene Rearrangement in a Patient with Right Colon Cancer

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Abstract

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity worldwide. Recent genome-scale molecular analyses have uncovered several potential therapeutic targets for this disease, including BRAF mutation, ERBB2 amplification, and neurotropic tropomyosin receptor kinase fusion gene. Gene rearrangements involving anaplastic lymphoma kinase (ALK) gene have been identified as oncogenic drivers in lung adenocarcinomas, and to be highly sensitive to selective kinase inhibitors. To the best of our knowledge, CRC harboring the ALK fusion gene has rarely been reported. Herein, we report a patient with right colon cancer harboring an ALK gene rearrangement and review the clinicopathologic features as well as potential therapeutic targeting of ALK-rearranged CRC in the literature.

Keywords: Anaplastic lymphoma kinase gene rearrangement, colorectal cancer, targeted gene sequencing

Introduction

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity worldwide, in which KRAS, BRAF, and PIK3CA mutations are commonly identified. Recently, genome-scale analyses have identified several potential therapeutic targets in CRC, including ERBB2 amplifications and gene fusions involving anaplastic lymphoma kinase (ALK), RET, ROS1, and neurotropic tropomyosin receptor kinase (NTRK).[1] Chromosomal translocations involving the ALK gene are most commonly found in nonsmall-cell lung cancer (NSCLC),[2] and a few studies have reported CRC harboring ALK gene fusions. Herein, we present a case of right colon cancer harboring an ALK gene rearrangement.

Case Report

We retrospectively reviewed the database of National Cheng Kung University Hospital, which contains clinical information

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and molecular profiling of 103 Stage III and high-risk Stage II CRCs to identify cases harboring ALK gene fusions. Somatic mutations in the database were determined using Oncomine™ Comprehensive Assay version 1 (Thermo Fisher Scientific Inc., Carlsbad, CA, USA), a targeted next-generation sequencing (NGS) assay.[3] Among these cases, only one case harboring an ALK gene rearrangement was identified. This case was a 53-year-old woman who had underlying chronic hepatitis B and old pulmonary tuberculosis. She presented to our gastroenterology surgery (GS) outpatient department (OPD) for colon cancer consultation in April 2008. The initial presentations were vague abdominal pain with a small caliber of stool and bloody tinged stool over 1-month period. The examination and blood work were unremarkable except for elevated carcinoembryonic antigen (CEA; 6.66 ng/mL) and carbohydrate antigen 19–9 (CA 19–9; 141.21 U/mL). Computed tomography of the abdomen and pelvis identified splenic flexure of colon wall thickening and a right hepatic cyst. Colonoscopy demonstrated an irregular-shaped tumor, about 2–3 cm in size, with friable tissue and easy oozing in the ascending colon near the hepatic flexure [Figure 1a]. A chest X-ray revealed no evidence of metastatic disease. She underwent extended right hemicolectomy with cecum preservation and partial hepatectomy (for a large liver cyst) on April 22, 2008. The gross finding of the specimen consisted of a segment of the colon (20-cm long). An ulcerated firm mass (3 cm × 3 cm × 2.5 cm) with an elevated margin was identified 6 cm away from one end. A total of 15 lymph nodes were dissected from the mesentery. The histological findings showed a moderately differentiated adenocarcinoma invading through the muscularis propria into the subserosa layer with 2 of the 15 dissected lymph nodes involving metastatic adenocarcinoma [Figure 1b]. Both section margins, the rest of the colonic mucosa, and appendix were unremarkable. The tumor node metastasis staging was pT3N1M0 (Stage IIIB). Further molecular characterization showed wild-type KRAS, NRAS, and BRAF. The result of microsatellite instability (MSI) testing was stable. In addition, immunohistochemical staining and fluorescence *in situ* hybridization confirmed positivity for ALK [Figure 1c and d]. The postoperative period was uneventful, and the levels of CEA and CA 19–9 both diminished. Adjuvant chemotherapy with mFOLFOX6 (folinic acid [400 mg/m^2], fluorouracil [2400 mg/m^2], and oxaliplatin [85 mg/m^2]) for 12 cycles was given. She reported Grade 3 numbness as a chemotherapy-related adverse event. She then received regular GS OPD follow-up and has been apparently disease free for the subsequent 10 years.

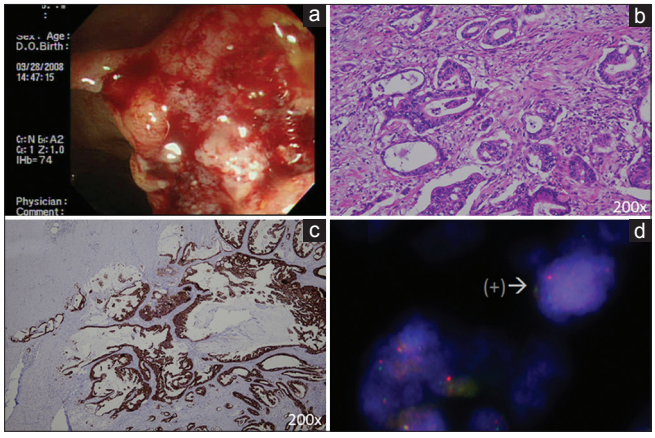

Figure 1: (a) The colonoscopic finding of the colorectal cancer patient with positive ALK gene rearrangement showed an irregular shape tumor, about 2–3 cm in size, with friable tissue and easy oozing in the ascending colon near the hepatic flexure. (b) The H and E stained images of primary colon tumor sections with positive ALK gene rearrangement showing a moderately differentiated adenocarcinoma with invasion into the subserosa layer. (c) Immunohistochemical staining with D5F3 anti-ALK antibody showing strong diffuse cytoplasmic staining. (d) The separated red and green probe signals by the FISH analysis indicating the presence of ALK gene rearrangement

Discussion

Chromosomal translocations and their corresponding gene rearrangements have significance in the initiation of tumorigenesis and have been strongly associated with distinct tumor subtypes.[4] The activation of proto-oncogenes by genomic rearrangements resulting in the fusion of two unrelated genes was identified in leukemias and lymphomas several decades ago. More recently, similar phenomena have been identified in a variety of solid tumors.[5] Among epithelial tumors, ALK gene rearrangements are more common in lung cancer, varying from 4% to 7%, and rare in breast, kidney, colorectal, esophageal, thyroid, ovarian, and bladder carcinomas.[6] ALK rearrangements are recurrent events and involve partner genes EML4, C2orf44, CAD, and the novel STRN, PPP1R21, SENPF, MAPRE3, as well as PRKAP1B.[7] These rearrangements can be identified by exon array profiling, FISH, and NGS.[8]

One study included a cohort of 27 metastatic colorectal carcinoma patients bearing ALK, ROS1, and NTRK rearrangements and reported clinical features and molecular characteristics including female predominance, median age of 55 years, right-sided primary tumor, wild-type RAS and BRAF mutations, and high MSI.[1] Another retrospective study which was designed to address ALK gene amplification in all stages of CRC reported equal gender distribution, higher percentage of patients aged more than 50 years, Stage I disease, poorly differentiated adenocarcinoma, positive BRAF mutations, wild-type KRAS mutations, and stable MSI (MS-S).[5] Both results suggest that ALK gene rearrangements and ALK amplification confer poor prognosis in CRC.

In our female patient, stage IIIB CRC was diagnosed when she was in the age of 53 years and had clinical features and molecular characters of a right-sided tumor, wild-type RAS, BRAF, MS-S, and EML4-ALK gene rearrangements. She survived beyond 10 years and had an apparently good outcome after surgery and adjuvant chemotherapy.

As with numerous other solid tumors, CRC is a heterogeneous disease in which different subtypes may be distinguished by

their specific clinical and/or molecular features. Recurrent genetic lesions committing oncogene addiction have recently been investigated as therapeutic targets.

The benefit of targeting ALK using tyrosine kinase inhibitors such as crizotinib and ceritinib in lung and inflammatory myofibroblastic tumors has been reported.[9] Patients positive for EML4-ALK lung adenocarcinomas have been reported to show around a 61%–74% response rate to the ALK inhibitor crizotinib.[10] Entrectinib, a selective pan-TRK, ROS1, and ALK inhibitors have been shown to have remarkable objective responses and clinical benefit in NSCLC in Phase I–II clinical trials.[2]

Recently, small studies on CRC have suggested an incidence of EML4-ALK translocations ranging from 0.4% to 2.4%. However, data regarding the effect of ALK inhibitors in treating CRC with EML4-ALK rearrangements are lacking. A novel CAD-ALK-rearranged gene was identified recently in CRC, for which pharmaceutical blockade with entrectinib had excellent clinical antitumor effects.[9,11]

Owing to the few cases of ALK rearrangements reported in CRC, evidence of the effectiveness of specific ALK therapeutic inhibition is insufficient. Further investigations are warranted to investigate the potential role of ALK inhibitors as a therapeutic agent in a subset of patients with CRC.

Conclusion

Colorectal carcinoma with ALK gene fusions represents a rare subtype of CRC with distinct clinicopathologic features. We present a woman with Stage III CRC harboring an EML4-ALK gene rearrangement who has been disease free for more than 10 years.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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