CASE REPORT

DNA Marker in Stool Led to a Second High-Quality Colonoscopy Within Three Months and Removal of an Undetected High-Risk Polyp

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SUMMARY

Background: In this case study, the patient first had a colonoscopy based on an incidental episode of vomiting and abdominal pain.

Materials and Methods: Two months after recovery, a multitarget stool test (ColoAlert®) was performed and showed a known somatic mutation in the oncogene KRAS, reported to be associated with colorectal cancer. As a result, a second complete colonoscopy was performed at another center.

Results: This procedure led to the diagnosis and removal of a later classified high-risk polyp that had been missed during the initial colonoscopy.

Conclusions: This case report shows the use of genetic markers in stool testing has the potential to detect colon cancer in very early stages when treatment is inexpensive and effective.


KEYWORDS

colorectal cancer, early detection, multitarget stool DNA test, non-invasive screening, precancerous lesions

INTRODUCTION

Colorectal cancer (CRC) has the third highest incidence of all cancers worldwide, and is the second most common cause of death, with 1.9 million new cases and 930,000 deaths reported in 2020 [1]. Although most CRCs are found in adults aged 50 years and older, there has recently been a considerable rise in early-onset CRC. At present more than 12% of total cases are diagnosed in individuals younger than 50 years old [1]. Based on evidence from epidemiological and pathological studies, most CRCs develop over time from the normal intestinal mucosa to precancerous advanced adenomas, then to a carcinoma and finally to an aggressive metastatic cancer [2]. This process is slow, normally progressing over years and, in some cases lasts more than 10 years. This transition is characterized by several genetic and epigenetic changes. The classical pathway (adenoma-carcinoma sequence) is characterized by ade-
nomatosis polyposis gene mutations or deletions leading to chromosomal instability driving the development of CRC [2]. Activating mutations of the KRAS and BRAF oncogenes and inactivating mutations of the TP53 tumor suppressor gene further promote adenoma-carcinoma progression. Recent studies [3] have shown a much more complex and diversified molecular progression towards CRC. There are at least four consensus molecular subtypes. Each subtype demonstrates both independent prognostic value as well as unique clinical, biological, and molecular signatures of the tumors. Additionally, increased mRNA expression profiles have recently been observed in both advanced adenomas and CRC samples. Interestingly, genes have been identified, that showed selective overexpression patterns unique to advanced adenomatous lesions [4].

A complete colonoscopy is accepted to have the greatest degree of sensitivity (> 90%) and specificity (100%) in diagnosing CRC or advanced adenomas and is the only procedure to offer the option of linking diagnostics and therapy by resection of detected lesions [5]. Recently, it has become evident that withdrawal time is a high-quality indicator for colonoscopy accuracy, especially for the early detection of adenomas, and other less protruding lesions, that can be easily overseen during colonoscopy [6].

Stool-based screening tests for early detection of CRC have many advantages compared to colonoscopy, being non-invasive and causing less discomfort, while having acceptable clinical performance and greatly improving patient compliance [6-8]. If the endoscopist is aware that a stool test is aberrant, it has been shown to have a beneficial impact on the diagnostic yield and quality of the subsequent colonoscopy [6].

We report a case, where a first colonoscopy was performed after an acute situation with abdominal pain and vomiting. A few months later, after performing the ColoAlert® test and finding a KRAS mutation in a stool sample, the patient had a second colonoscopy at another clinic. The endoscopist performed the procedure with a significantly longer withdrawal time and identified a polyp that was initially missed. Polymerase Chain Reaction (PCR) was then performed and confirmed the genetic evidence of a high-risk polyp.

**CASE REPORT**

In early January 2022, a 60-year-old man with a 10-year history of medically controlled hypertension and diabetes type 2 presented with acute abdominal pain, chills and vomiting. Ibuprofen relieved the symptoms. Two weeks later he was admitted for a combined gastroscopy and colonoscopy, identifying antrum gastritis and hiatus hernia, whereas the colon was described as normal. Colonoscopy was performed since his regular CRC screening was overdue by many years. He recovered completely without treatment. Two months later, as part of a company health program, the patient performed a multitarget stool test (ColoAlert®, Mainz Biomed Germany GmbH, Mainz, Germany), aimed at early detection of colorectal cancer and its precursors. The test result was positive for the oncogene KRAS. The mutation was found in somatically mutated remnant cells found in the stool sample. ColoAlert® tested negative for BRAF, total human DNA and the FIT (Fecal Immune Test) for species-specific human hemoglobin.

Based on this observation, he performed a new combined gastroscopy and colonoscopy. The withdrawal time for the repeated procedure was about twice as long compared to the first endoscopy, as the suspicion for abnormalities was raised by the ColoAlert-based genetic diagnostic result. During the procedure, a polyp of 8 mm was observed in the rectosigmoid transition area and was removed (shown in Figure 1). There were no other signs of pathology in the colon. After removal, histology and genetic analysis showed a hyperplastic polyp also with a KRAS mutation (G13D), as in the original stool sample. The lesion was classified accordingly as a high-risk polyp.

Six months later, the ColoAlert® test was repeated, and results were negative.

**DISCUSSION**

Based on this report, and supported by scientific evidence [6], knowledge of a positive multitarget stool DNA test may improve both the diagnostic yield and the quality of the subsequent colonoscopy. Significantly more precancerous lesions and more polyps per patient were detected when endoscopists were informed of aberrant stool DNA results compared with findings in a blinded group [6]. Additionally, the median colonoscopy withdrawal time was significantly longer in the unblinded group. Unfortunately, the populations’ compliance with screening methods for early diagnosis of colorectal cancer has been limited in the past, with only 40% of women and 18 - 20% of men currently undergoing testing by colonoscopy [9]. Since people with aberrant DNA signatures or blood in stool are at a higher risk for developing CRC or a precursor lesion of such, ColoAlert® and similar diagnostic stool tests may be used as a triage tool to determine who urgently needs a high-quality colonoscopy. Stool tests are easy to collect, easy to perform and have a high degree of acceptance compared to colonoscopy [9]. The combination of signatures from genetic changes (early warning sign) with microscopical bleeding (FIT, normally a later warning sign) gives these novel and innovative tests a performance characteristic that are close to those of regular colonoscopy [7,8].

The patient described above was tested as part of a company health program and was included based on age and metabolic syndrome as two independent risk factors. Incidentally, due to a transient episode of abdominal pain and vomiting, he had a first colonoscopy, described as
normal, a few months earlier. Based on the aberrant signature of KRAS in ColoAlert, he was referred for a new colonoscopy that resulted in the removal of an undetected lesion showing the same genetic transformation in the KRAS oncogene. Typically, polyps below 1 cm in diameter are not considered as high-risk lesions. For the patient in this case study, the same KRAS mutation that was found in stool, was observed in the polyp, supporting the classification of this polyp as a high risk of future malignant transformation.

Regarding CRC screening, there are variations in guidelines between countries. For the United States [9], the US Preventive Services Task Force recommends several screening strategies, including stool tests, flexible sigmoidoscopy, colonoscopy, and CT colonography (virtual colonoscopy). Based on current guidelines, we could expect that the patient would have been recommended to have his next screening colonoscopy after 10 years. Therefore, it is likely that the high-risk polyp would have progressed to a fatal outcome within that timeframe.

In conclusion, our report shows that the use of genetic markers in stool testing, such as ColoAlert®, help in triaging patients that really need a high-quality colonoscopy. It also emphasizes the need of sufficient withdrawal-time to be able to detect as many lesions as possible that are at high risk for further malignant transformation.

**Statement of Ethics:**
No ethical approval was obtained because this study did not involve a prospective evaluation. The authors wish to thank the patient for his eagerness to participate. Written informed consent was obtained from the patient for publication of the details of this medical case and any accompanying images.

**Data Availability Statement:**
All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

**Source of Funds:**
The authors declare that no funding was received for this study.

**Declaration of Interest:**
Susanne Franck has no conflict of interest. Moritz Eidens is CSO, director and shareholder in Mainz Biomed N.V. Jürgen Fuhrländer is a clinical advisor and shareholder in Mainz Biomed N.V. Dagfinn Ogreid is a clinical advisor and shareholder in Mainz Biomed N.V.
References:


2. Global Cancer Observatory. [cited 2022 Sep 21]. https://gco.iarc.fr/


