Case Report

DNA signature and occult blood in stool led to diagnosis of an early-onset metastatic rectal cancer in a young pregnant woman: a case report

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Background: Colorectal cancer (CRC) is the third most common form of cancer worldwide in terms of incidence and the second in terms of mortality with 1.9 million new cases and 930,000 deaths reported in 2020. Corresponding numbers in the U.S. are 150,000 and 53,000, respectively. Although the majority of CRCs in the U.S. and other high-income countries are in adults aged 50 and older, there has recently been a considerable rise in early-onset CRC, so that 17,930 cases in the U.S. (12% of total cases) are diagnosed in individuals younger than age 50, representing the equivalent of 49 new cases per day. Early diagnosis is essential to improve the prognosis and reduce the number of cancer-related deaths. Here we report the case of a young pregnant woman, who was diagnosed with CRC with the help of the ColoAlert™ multitargeted stool test.

Case Description: In this case study, a young pregnant woman presented with obstipation, rectal bleeding, and pelvic pain, symptoms that were ascribed to her pregnancy. On her own, she performed a multitarget stool test (ColoAlert™) that showed occult blood as well as a very high level of human DNA, both known to be associated with presence of CRC. After testing, she was referred for rectoscopy (during her 21st week of pregnancy), which showed an exophytic, semicircular tumor 10 cm from anus in the rectosigmoid junction. Histology confirmed adenocarcinoma in rectum. Further examination showed perirectal infiltration as well as metastases to both liver and adrenal gland.

Conclusions: This case report shows the importance of considering CRC as a possible diagnosis in young people. It also demonstrates the usefulness of multitarget stool testing that in this case led to the endoscopic confirmation of the diagnosis followed by an immediate start of potential life-saving treatment.

Keywords: Non-invasive colorectal cancer screening (non-invasive CRC screening); DNA stool test; oncogenes; DNA signature; case report

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Introduction

Colorectal cancer (CRC) is the third most common form of cancer worldwide in terms of incidence and the second in terms of mortality with 1.9 million new cases and 930,000 deaths reported in 2020. Corresponding numbers in the U.S. are 150,000 and 53,000, respectively (1). Although the majority of CRCs in the U.S. and other high-income countries occur in adults 50 years of age and older, there

has been a significant recent increase in cases of early-stage colorectal cancer, with 17,930 cases (12% of total cases) diagnosed in people under 50 in the U.S., or 49 new cases per day (2,3). There are several clinical differences in CRC between early- and later-onset of the disease (3). Early-onset CRC are most common in rectum, followed by the distal colon (accounting together for about 70% of the total cases). Late-onset CRC occurs at similar frequency in proximal colon and distal colorectum. CRC is higher among men than women, whereas females are more likely to acquire early-onset rectal cancer. Poorly differentiated cancers and cancers with signet-ring cells are also more common among patients with early-onset disease. Epidemiologic and pathologic studies indicate that most colorectal cancers progress over time from normal colon mucosa to precancerous advanced adenomas, then to carcinoma, and finally to aggressive metastatic cancer (*Figure 1*) (4).

This process is slow and usually takes years, in some cases even more than 10 years. This transition is characterized by several genetic and epigenetic changes. The classical pathway (adenoma-carcinoma sequence) is characterized by mutations or deletions of the adenomatosis-polyposis gene that lead to chromosomal instability and promote the development of CRC. Activating mutations of the oncogenes *KRAS* and *BRAF* and inactivating mutations of the *TP53* tumor suppressor gene further promote adenoma-carcinoma progression. A recent study (5) has shown that the molecular course of colorectal cancer is much more complex and diverse and that there are at least four molecular consensus subtypes. Each subtype has been shown to have independent prognostic value as well as unique clinical, biological and molecular signatures of the tumors. Although most molecular changes are similar between the different age-groups, some differences are starting to be identified. Microsatellite stable (MSS) cancers were similar in all age groups, while *APC*, *KRAS* and *BRAF* mutations are more common in the late-onset group and *TP53* alterations are most common among the younger group (3,5). The most common symptoms (3) at presentation with early-onset disease are hematochezia (38%), abdominal or pelvic pain and bloating (33%) and change in bowel habits (20%). These are all symptoms commonly associated with tumors of the rectum and left colon. Patients, as well as their primary health care providers, are often unaware of early-onset disease and its symptoms, and attribute it to common physiological or benign conditions. Stool-based tests for diagnosis and screening for CRC have been used for many years and can also be used to triage young patients that should be referred for endoscopy. These multitarget stool tests are non-invasive, cause little discomfort, have an acceptable clinical performance, and are well accepted by patients (6-9).

We here report a case where a young pregnant woman with symptoms that should have led to further actions, were ignored due to age and pregnancy. After a multitarget stool test showed a DNA signature commonly associated with CRC, the necessary actions were taken, and treatment started immediately after diagnosis of metastatic rectal cancer. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-136/rc).

Highlight box

Key findings

- This case report shows the importance of considering colorectal cancer as a possible diagnosis in young people.

What is known and what is new?

- Colorectal cancer (CRC) is the third most common form of cancer worldwide. The majority of CRCs in the U.S. and other high-income countries are in adults aged 50 years and older. More and more young people are developing early-onset CRC.
- Early diagnosis is essential to improve the prognosis and reduce the number of cancer-related deaths.

What is the implication, and what should change now?

- This case report demonstrates the usefulness of multitarget stool testing that led to the endoscopic confirmation of the diagnosis followed by an immediate start of potential life-saving treatment.

Case presentation

In February 2022, a previously healthy, 34-year-old woman got pregnant for the third time. After 4 months of pregnancy, she started suffering from obstipation, rectal bleeding, and pelvic pain. She complained repeatedly to her general practitioner that ascribed her symptoms to the ongoing pregnancy. On her own initiative, she performed a multitarget stool test (ColoAlert™, Mainz Biomed Germany GmbH, Mainz, Germany), which is used for the early detection of CRC and its precursors. The test result was positive for occult blood in stool. The immunological fecal occult blood test result (iFOBT) was determined to 958.27 µg/g (limit 5 µg/g) and human DNA was found to be 40,300 pg/µL (limit 1,000 pg/µL), whereas the test was negative for mutations in the oncogenes *KRAS*

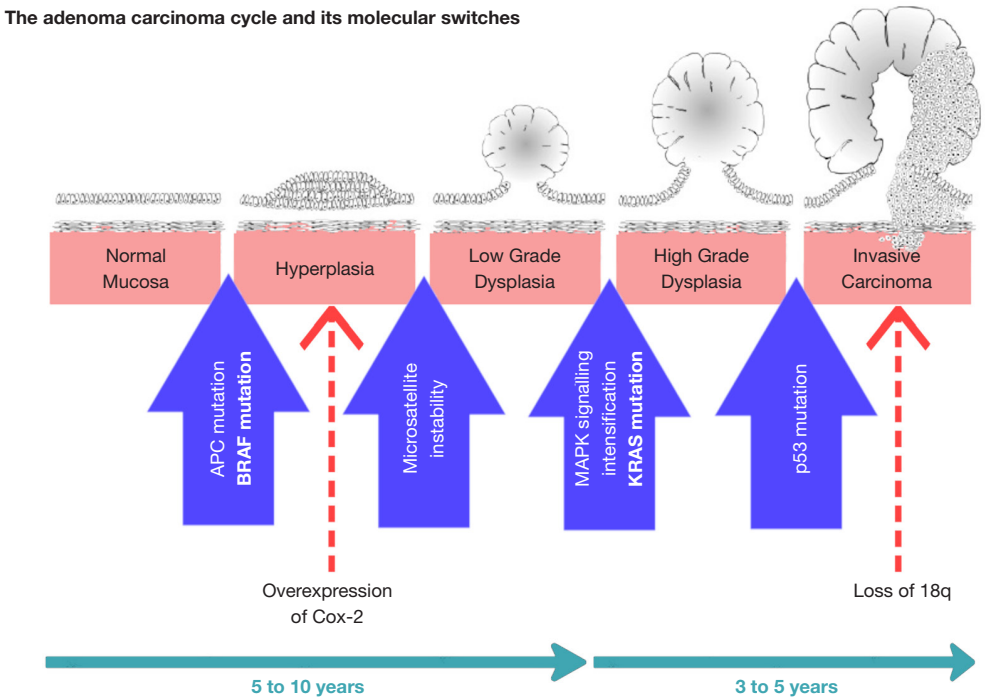

Figure 1 The molecular switches in the adenoma carcinoma sequence, coupled to its timely progression.

and *BRAF*. Due to these findings in stool, she was now referred for rectoscopy (during her 21st week of pregnancy), which showed an exophytic, semicircular tumor 10 cm from anus in rectosigmoid junction. Histology confirmed adenocarcinoma in rectum. Further examination showed perirectal infiltration as well as metastases to both liver and adrenal gland. She had caesarean section in her 28th week of pregnancy. The newborn was routinely treated in the intensive care unit for premature babies and developed normally. Later she received 2 months of neoadjuvant FOLFOX chemotherapy (folinic acid, fluorouracil, oxaliplatin) followed by local radiotherapy (5× 5 Gy). Two months later she performed extensive surgery (rectum resection, removal of left adrenal gland and liver resection (segment 2/3) and cholecystectomy. Resection was R0 and histological classification was pT3pN1apM1b (liver, adrenal). Three months after surgery she had no sign of recurrence.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Although the frequency of hereditary CRC (3–5% of overall prevalence in early-onset disease) is higher in young people, it has been estimated that above 70% of all early-onset cases are "sporadic". Early-onset disease occurs in younger people, and they present a more aggressive disease pattern. They tend to be diagnosed with more advanced-stage disease, which is associated with increased mortality as well as more extensive surgical and medical treatment. The most marked increase in early-onset disease has been seen among non-Hispanic white persons. Risk factors ranked, based on relative risk data from highest to lowest, include a Western dietary pattern (ultra-processed food), smoking, consumption of red meat, obesity and overweight as well as frequent use of antibiotics (3). The change in dietary pattern, as well as the use of antibiotics, is thought to facilitate malignant CRC progression through changes in gut microbiota composition. To make it even more complicated, putative risk factors for early-onset disease identified in case-control studies overlap with established risk factors for late-onset disease.

For first-line primary health-care providers, it is important the occurrence of early-onset CRC is part of the mind-set in the clinical evaluation of this patient group.

There is an urgent need for increased awareness of such early-onset cancers both for the younger patients and their health-care providers. In addition, first-line health care providers should be mindful of the burden that this disease represents with respect to treatment-related side effects, including sexual dysfunction, infertility, as well as financial and psychosocial consequences. It is not only CRC that shows an alarming increase in young people. Over the past three decades cancer rates in general in the G20 group of industrialized nations have increased faster for 25- to 29-year-old than any other group; by 22% between 1999 and 2019. Rates for 20- to 34-year-old are now at their highest level in 30 years, whereas in contrast, cases in those over 75-year-old have declined from their peak in 2005 (2). For first-line health-care workers, it is most important to listen carefully to the story of the patient. In cases of suspicion or possibility of an early-onset CRC, there are several simple tests that can facilitate a correct diagnosis. Since there is a dominance of rectal cancers in this group, many of them can be reached by rectal manual examination or seen by anoscopy/proctoscopy. Macroscopic or microscopic blood in stool might be a warning sign as well as elevated levels of serum carcinoembryonic antigen.

Because people with abnormal DNA signatures in their stool are at higher risk of developing or presenting with colorectal cancer, ColoAlert™ and similar diagnostic stool tests should be used as a triage tool to determine who is in urgent need of a high-quality colonoscopy. Stool tests are easy to collect, simple to perform and have a high acceptance rate compared to endoscopy (8,9). It was the combined finding of occult blood and an extremely high level of human DNA in stool that led to further examinations and the correct diagnosis in this case.

The incidence of early-onset CRC is forecast to increase steadily and more than double by 2030 (2,10). There are a high number of delayed diagnoses in younger patients that present with advanced disease stages, as shown in this case report. This underscores the need for greater awareness of early-onset CRC both in the public, as well as with first-line health-care professionals. An important improvement is that the United States Preventive Service Taskforce has reduced screening age for CRC to 45 years instead of 50 years (11).

Conclusions

Patient and public education is a key factor in reducing the unnecessary suffering and fatalities of such diseases. Another is the further development of simple laboratory testing, like the multitarget stool test that can facilitate the differentiation between those who suffer from cancer and those with a benign or physiological condition behind otherwise identical symptoms. This case report shows the importance of considering CRC as a possible diagnosis in young people, especially as described in this case report, where rectal bleeding is not a 'normal' side effect of a pregnancy. Regardless of this, any type of rectal bleeding (with or without additional specific symptoms) must be considered potentially CRC related and consequently thoroughly investigated.

It also demonstrates the usefulness of multitarget stool testing that in this case led to the endoscopic confirmation of the diagnosis followed by an immediate start of potential life-saving treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-136/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-136/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-136/coif). M.E. reports that he is CSO, director and shareholder in Mainz Biomed N.V. and is employed at Mainz Biomed Germany GmbH. J.F. reports that he is shareholder at Mainz Biomed N.V and serves as an employee for Mainz Biomed GmbH. D.Ø. receives consulting fees from Mainz Biomed Germany GmbH and is clinical advisor and shareholder at Mainz Biomed N.V. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised

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