

CASE REPORT

A new germline mutation in *BRCA1* in a Chinese family with gynecologic cancers and colon cancer mimicking ovarian cancer: A case report

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Abstract

BRCA1 is a key player in the homologous recombination DNA repair process. Pathogenic *BRCA1* germline mutations confer a high risk of breast and ovarian cancers. Nevertheless, the association between *BRCA1* mutations and colorectal cancer (CRC) risk remains unclear. While *BRCA1* alterations significantly influence diagnosis and therapeutic decisions in breast and ovarian cancer, including the use of FDA-approved poly (ADP-ribose) polymerase (PARP) inhibitors, their role in CRC management is less established. Here, we present a case of a 57-year-old female diagnosed with CRC and a family history of ovarian and endometrial cancers. All her cancer-affected family members, including herself, were found to carry two germline *BRCA1* mutations, including a novel mutation (c.212+2T>G) that has not previously been reported in CRC. The proband exhibited peculiar clinicopathological and molecular features, including a CK7-positive/CK20-negative immunophenotype that mimicked an ovarian origin. The patient received five cycles of nab-paclitaxel plus carboplatin, followed by maintenance therapy with the PARP inhibitor (PARPi) niraparib. This case provides real-world evidence supporting the pathogenicity of the *BRCA1* c.212+2T>G mutation and highlights the potential of PARPi therapy in CRC patients harboring *BRCA1* mutations. Further, it demonstrates the possibility of a rare immunohistochemical phenotype in CRC cells harboring a deleterious *BRCA1* mutation.

Keywords: *BRCA1* germline mutation; Colorectal cancer; Rare immunophenotype; Family history

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1. Introduction

BRCA1 is a tumor suppressor gene that participates in multiple cellular processes, including DNA repair, cell cycle checkpoint surveillance, transcription regulation, and apoptosis. It plays a key role in homologous recombination (HR), an error-free mechanism for repairing DNA double-strand breaks caused by internal and exogenous

agents.¹⁻³ However, mutations in *BRCA1* may lead to an impaired HR process, generating genomic instability and oncogenesis. Germline mutations in *BRCA1* are associated with high penetrance for breast and ovarian cancers, with reported lifetime risks of up to 85% and 40%, respectively, in carriers of pathogenic variants.^{4,5} In contrast, the risk of colorectal cancer (CRC) was not significantly increased in *BRCA1* and/or *BRCA* mutation carriers.⁶

CRC is the third most diagnosed cancer type worldwide.⁷ Most CRC cases are sporadic with no apparent genetic predisposition or family history, while approximately 5–10% of the cases are hereditary.⁸ However, there is limited understanding of the role played by *BRCA1* mutations in CRC, although reports show individuals with hereditary breast and ovarian cancer family history have a greater chance of developing CRC.^{9,10} A number of studies examined the incidence of CRC in *BRCA1* mutation carriers, but findings have been inconsistent.¹¹

The *BRCA1* gene harbors a wide distribution of mutations throughout its coding regions. With the rapid development of sequencing technologies, hundreds of deleterious mutations of *BRCA1* have been reported, many of which are highly ethnic-specific.¹² For example, c.66_67delAG and c.5263_5264insC occur in 1% of Ashkenazi Jews, c.3627insA is found in 10% of Korean ovarian cancers, and c.5154G >A occurs in 5.6% of the Chinese population.^{4,13,14}

In addition to the association between pathogenic mutations in *BRCA1* and increased risk of cancer development, germline loss-of-function (LOF) in *BRCA1* also plays an important role in diagnostic and therapeutic decisions. Several studies have systematically investigated the clinicopathological and molecular characteristics of *BRCA1* mutation carriers, revealing differences compared to wild types.¹⁵ For example, Grinshpun *et al.*¹⁶ found that *BRCA1* mutations increase the chance of mucinous histology in CRC, and gene signatures in some *BRCA1*-mutated CRCs showed a significant correlation with basal-like breast cancer. In the case of therapy selection for carriers of *BRCA1* germline mutation, HR-deficient cells are more susceptible to DNA damage, making *BRCA1* mutation carriers more responsive to platinum-based chemotherapies.¹⁷ Platinum reinduction may be considered for BRCA-positive, platinum-resistant ovarian cancer patients to prolong progression-free survival).¹⁸ Conteduca *et al.* reported a considerable clinical activity of melphalan chemotherapy, particularly in a subset of patients with *BRCA1/2* mutations.¹⁹ The development of targeted therapies has further improved outcomes in *BRCA1*-related cancers. Poly (ADP-ribose) polymerase inhibitors (PARPi) have shown favorable responses in such

cases. PARP enzymes repair single-strand DNA breaks through the base excision repair pathway; in HR-deficient cells, this leads to the accumulation of DNA damage and cell death through a mechanism known as synthetic lethality.²⁰

In this report, we present the case of a 57-year-old woman diagnosed with CRC, exhibiting distinct clinicopathological and molecular features. She has a family history of *BRCA1*-associated ovarian and endometrial cancers.

2. Case presentation

In 2018, a 57-year-old female initially experienced a change in bowel habits, blood in the stool, and intermittent abdominal pain. Her medical history included hypertension, type II diabetes, and cerebral infarction involving the left thalamus and posterior limb of the internal capsule, for which she received anticoagulation and cerebrovascular function therapy. In 2020, she was diagnosed with stage III colon cancer (cT4aN+M0). Tumor marker testing revealed the following values: HE4, 39.5 pmol/L; AFP, 1.78 IU/mL; CEA, 1.86 µg/L; CA19-9, 18.81 U/mL; CA242, 6.07 U/mL; SCC, 0.37 ng/mL; CA50, 8.10 U/mL; CA72-4, 3.13 U/mL; NSE, 6.57 ng/mL; Cy21-1, 1.85 ng/mL; and ferritin, 135.3 ng/mL. Two tumor markers were significantly elevated: CA125 at 338.7 U/mL and CA15.3 at 31.7 U/mL. Colonoscopy showed ulcers at the rectosigmoid junction (Figure 1A). Further, computed tomography (CT) in October 2020 showed irregular, asymmetrical thickening of the descending colon wall, followed by multiple enlarged lymph nodes (Figure 1B). Consequently, the patient was hospitalized for laparoscopic colon resection with lateral lymph node dissection

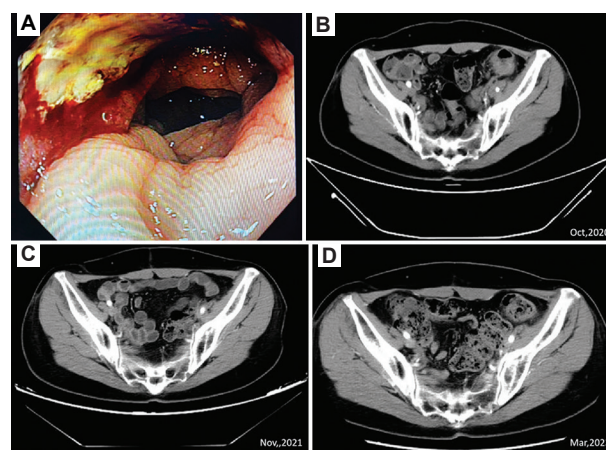


Figure 1. A case of colorectal cancer with distinct clinicopathological features. (A) Image from the colonoscopy. (B) Computed tomography scans on the first examination, (C) second follow-up, and (D) the past follow-up.

in November 2020. The post-operative pathological examination of the resected specimen revealed a 3 × 2 cm invasive, poorly differentiated, high-grade serous-like sigmoid tumor, staged as pT4aN2M1 (stage IV) (Figure 2A). Immunohistochemical staining showed positive but limited expression of cytokeratin 7 (CK7), chromogranin A (CgA), and CD34, while caudal type homeobox 2 (CDX-2), CK20, SATB2, and GATA binding protein 3 (GATA3) were negative (Figure 2B and C). The Ki-67 proliferation index was elevated at 60%. However, right after the surgery, tumor marker levels did not decrease as expected: CA125 slightly decreased from 338.7 U/mL to 298.4 U/mL, while CA15.3 increased from 31.7 U/mL to 41.4 U/mL.

To further explore the tumor's molecular characteristics, DNA was extracted from formalin-fixed paraffin-embedded tumor tissue and matched peripheral blood leukocytes for control. Genomic libraries were constructed using DNA fragments sheared to 150–200 bp, and targeted next-generation sequencing (NGS) was performed using a 121-gene panel (Genetron Health Co., Ltd., China), achieving a mean coverage depth of 500×. NGS data were analyzed using the in-house bioinformatics pipeline through alignment to the human reference genome assembly. Three tumor mutations were detected: Somatic *TP53* c.637C>T and two germline *BRCA1* variants, c.212+2T>G and c.5123C>T. No mutations were detected in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*).

Given the immunophenotypic profile and the presence of germline *BRCA1* mutations, the possibility of an ovarian origin was considered despite the lack of overt ovarian lesions on pre-operative positron emission tomography-CT (PET-CT) and intraoperative exploration. A repeat PET-CT in December 2020 revealed a hypermetabolic nodule in the outer quadrant of the left breast at the level of the nipple (Figure A1). No other abnormal fluorodeoxyglucose uptake was noted. Immunohistochemical analysis of the breast biopsy showed the following: Ki67 (70%+), P63

(-), CK7 (+), CDX-2 (-), ER (-), PR (-), SMA (-), calponin (-), Her-2 (focal 1+), desmin (-), NapsinA (-), WT1 (-), CD125 (+), P40 (-), villin (-), CK (+), CD56 (+), SyN (+), CgA (-), PAX8 (-), mammaglobin (-), and GCDFP-15 (-). An elevated Ki67 index, indicating a pathognomonic nature of proliferating cancer cells, was noted. However, further laboratory examination showed no malignant cells in the breast biopsy. Despite the absence of a primary mammary lesion, the patient had a strong family history of *BRCA1*-associated malignancies. Three of her sisters had been diagnosed with either ovarian cancer or high-grade breast cancer. Interestingly, common CRC markers, such as CEA and CA19-9 remained consistently within normal limits, raising further doubt about the initial CRC diagnosis. Subsequently, the patient was suspected of metastatic ovarian cancer with intestinal dissemination. It was believed that the disease demonstrated as colorectal cancer phenotypically, though ovarian cancer genetically, considering both the pathogenicity of the *BRCA1* mutation carried by this proband and the family history of cancer. Given these clinicopathological features, the patient was treated with standard adjuvant chemotherapy: Nab-paclitaxel (175 mg/m² IV over 3 h) and carboplatin (AUC 5–6 IV over 1 h) administered every 21 days for five cycles (Figure 3). Imaging in March 2021, including MRI, CT, and ultrasound, was performed to evaluate the efficiency of treatment, revealing the resolution of the previously detected breast nodule. Thereafter, the patient underwent a maintenance therapy of PARPi niraparib (300 mg/day), and no recurrence of any kind has been observed (Figure 1C and D).

While the family history did not include colon cancer cases, several other tumor types were present. For example, the patient's father, who died at 65, had been diagnosed with gastric cancer. In addition, both the eldest and third-oldest sisters were diagnosed with ovarian cancer, and the latter has already passed away (Figure 4). In view of the presence of the germline *BRCA1* mutation in this proband and her family history, genetic counseling was conducted

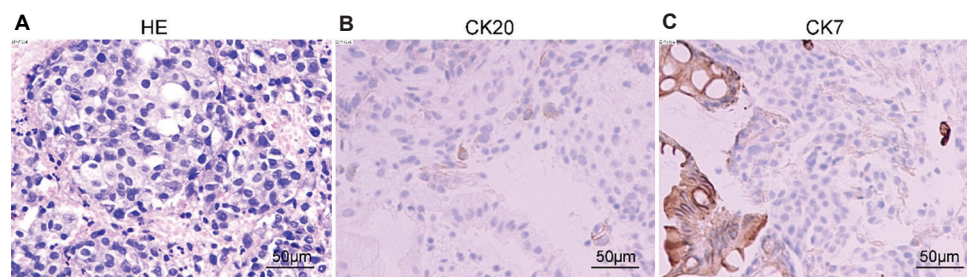


Figure 2. Immunohistochemical analysis of the primary colon cancer specimen. (A) Hematoxylin and eosin-stained section of the primary colon cancer specimen demonstrating poorly differentiated, high-grade serous-like carcinoma. (B and C) Immunohistochemical staining of the excised specimen showing weak positive for CK7 and negative for CK20; magnification: ×200. Scale bar: 50 μm.

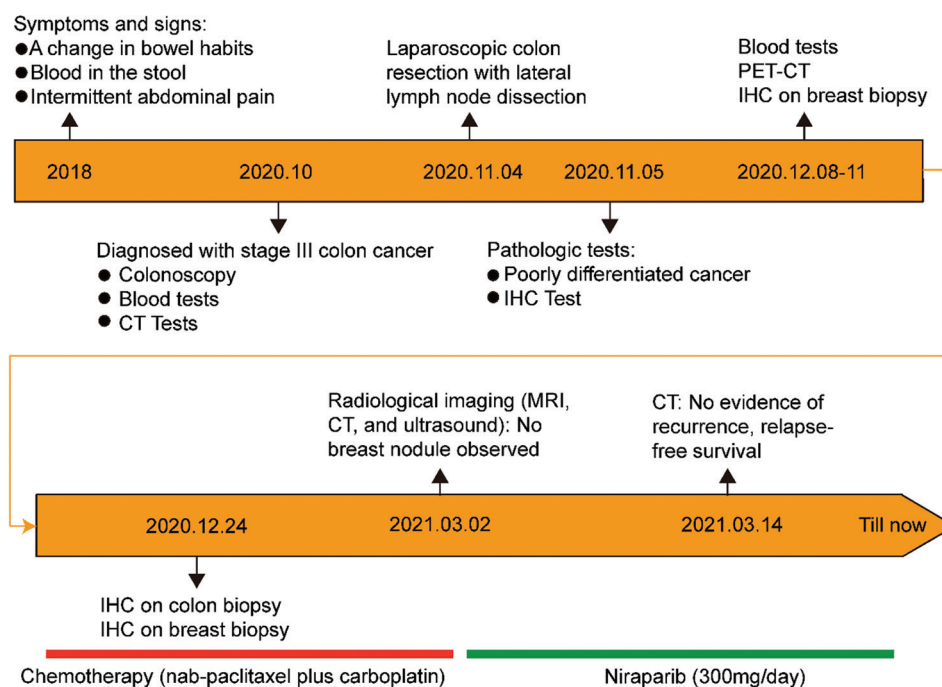


Figure 3. Treatment timeline of the patient. Red bar indicates the period of chemotherapy, comprising of nab-paclitaxel (175 mg/m² IV over 3 hours) and carboplatin (AUC 5–6 IV over 1 hour) administered every 21 days for five cycles. Green bar indicates the period of targeted therapy with niraparib, which has continued to date without evidence of tumor progression.

Abbreviations: AUC: Area under the curve; CT: Computed tomography; IHC: Immunohistochemistry; PET-CT: Positron emission tomography-computed tomography.

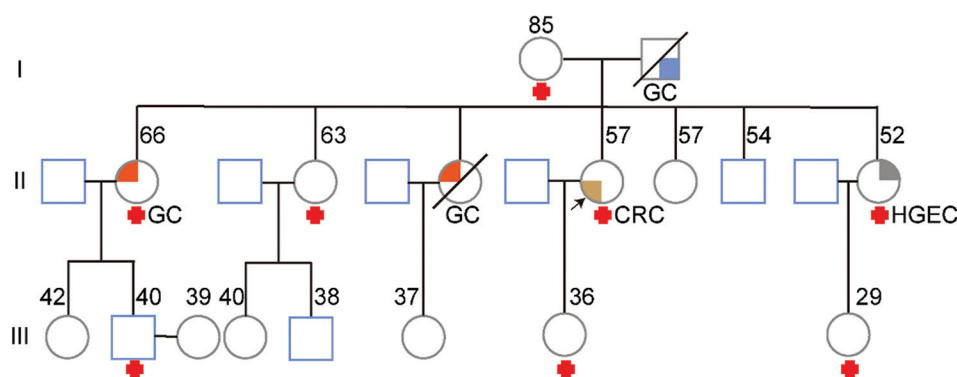


Figure 4. Familial pedigree of the case. The proband is indicated by an arrow. Squares and circles represent males and females, respectively. The diagonal slash indicates members of the family who have passed away. Ages (in years) are shown for family members who were tested for *BRCA1/2* gene mutations. Red crosses indicate the carriers of *BRCA1* mutations: c.212+2T>G and c.5123C>T. All family members diagnosed with cancer are annotated as follows: colorectal cancer, gastric cancer, high-grade endometrial cancer and ovarian cancer.

involving 14 relatives with informed consent. After a full-gene analysis of *BRCA1/2*, two germline mutations in *BRCA1*, c.212+2T>G and c.5123C>T, were detected in the proband's mother, four out of seven siblings, and three of eight third-generation relatives tested. The younger sister, who was aware of the potential risks, agreed to undergo a medical examination and was diagnosed with high-grade

endometrial cancer. Both cancer-affected sisters tested were carriers of *BRCA1* germline mutation; samples from the deceased sister were not available for analysis. In addition, three third-generation carriers were offspring of three affected second-generation individuals (including the proband), suggesting maternal inheritance of the *BRCA1* c.212+2T>G and c.5123C>T mutations.

3. Discussion

The *BRCA1* gene is located on chromosome 17q21 and consists of 24 exons.²¹ Extensive efforts have been made to explore and determine the mutational status of the *BRCA1* gene considering the crucial role it plays in maintaining genome stability. Hundreds of mutations have been identified, over 80% of which result in truncated proteins. The others include missense mutations, splicing site variants, and regulatory region variants.²² In the present familial case, NGS detected two heterozygous germline variants in *BRCA1*: c.212+2T>G and c.5123C>T.

The *BRCA1* c.5123C>T (p. Ala1708Val) variant is a missense mutation located in exon 17. It has previously been reported in individuals with different cancer types, including breast, ovarian, and kidney cancers. A few studies have suggested that this variant affects protein stability and activity, while others indicate normal function.^{23,24} According to the ClinVar database¹, the present classification of c.5123C>T is a variant of uncertain significance. However, a different substitution at the same codon (p.Ala1708Glu) has been defined as pathogenic.

Compared with c.5123C>T, the *BRCA1* c.212+2T>G variant is a splice site mutation with limited interpretation, as only a single publication has mentioned this variant as functionally abnormal using the saturation genome editing (SGE) assay of *BRCA1*.²⁵ A similar substitution at the same codon, c.212+2T>C, has been reported in familial breast and ovarian cancers.²⁶ According to the American College of Medical Genetics and Genomics, intronic variants within 10 base pairs of an exon can have a strong influence on mRNA splicing. Multiple bioinformatic tools, including PolyPhen-2 and SIFT, predicted c.212+2T>G to be deleterious. Moreover, this variant is absent in major population databases, such as 1000_CN, 1000_MAF, ESP6500, and gnomAD. Coupled with the co-segregation of the variant in affected family members, the evidence supports a classification of “likely pathogenic”.²⁵

Several recent studies have shown the differences in *BRCA1* mutations among different populations through screening and data mining. There is a general agreement that germline mutation in *BRCA1* is ethnic-specific.¹³ Bhaskaran *et al.*²⁷ concluded that considering statistics of Caucasian populations as a global standard does not apply to Chinese populations. For example, some high-frequency founder mutations in non-Chinese populations were absent in the Chinese ethnicity. Conversely, many mutations in *BRCA1* were found exclusively in Chinese populations. In this case, the detection of c.212+2T>G in a Chinese family contributes to the growing *BRCA1*

mutation database relevant to this population. The presence of both c.212+2T>G and c.5123C>T variants in individuals with a family history of ovarian, endometrial, and colorectal cancers (CRC) suggests a pathogenic role for one or both mutations.

LOF mutations in *BRCA1* are well-established risk factors for breast and ovarian cancer. However, the prevalence of CRC in germline *BRCA1* mutation carriers remains debatable. Phelan *et al.*¹⁷ observed a meaningful increased risk of CRC in female carriers of *BRCA1* mutations based on 21 CRC cases. Further, similar findings have also been reported in a prospective study of over 7000 female *BRCA1/2* mutation carriers—a significantly higher risk of CRC existed in female carriers younger than 50.⁶ Oh *et al.* systemically analyzed 18 studies and also reached a similar conclusion.²⁸ More recently, Cullinane *et al.* performed a systematic review of 11 studies and a meta-analysis of nine studies, concluding that there was no association between CRC risk and *BRCA* mutation.²⁹ Although the proportion of familial CRC was previously reported to be up to 10% among all incidents, a study by Fuchs *et al.*³⁰ involving 32,085 men and 87,031 women found that genetic factors contributed to 23% of CRC cases diagnosed before age 45, with a relative risk of 1.72 in individuals with first-degree relatives affected by CRC. This finding aligns with Lee *et al.*,³¹ who also observed a familial risk in the general population. The discrepancies in the reported CRC risk among *BRCA1* mutation carriers may stem from the biased selection of high-risk cases with a family history of breast or ovarian cancers in some studies.

Although the risk of developing CRC in *BRCA1* mutation carriers is still unclear, CRC is observed with a higher frequency in hereditary ovarian and breast cancer families.^{32,33} Soyano *et al.* have reported a male carrier of a germline *BRCA1* mutation, who was diagnosed with colon cancer at the age of 33 while having a history of breast and colon cancers in his maternal and paternal relatives, respectively.² Moreover, a 20-year-old man affected with CRC was found to carry a germline *BRCA1* mutation; he was also reported to have a maternal family history of gastric and ovarian cancers and a paternal family history of colon and lung cancers.³² Xu *et al.* conducted a pedigree analysis of Lynch syndrome probands and found that *BRCA1* mutation carriers had a higher risk of developing different cancers, including colon, ovarian, and endometrial cancers.³⁴

At present, there is a lack of formal guidelines or recommendations for CRC screening for *BRCA1* mutation carriers. Therefore, the present case illustrates the importance of genetic testing, especially *BRCA1*,

¹ <https://www.ncbi.nlm.nih.gov/clinvar/>

in screening and identifying high-risk cancer carriers. Immunohistochemistry has been widely accepted as a tool for the correct diagnosis of tumor origin.^{35,36} An extensive study of the expression pattern of CK7/CK20 led to the discovery of the most commonly used immuno-markers for distinguishing between primary and metastatic CRC.³⁷ Normally, CK7 is expressed in the female genital tract, breasts, lungs, and urinary tract, while the expression of CK20 is observed in the tumors of the urothelium, Merkel cell, and gastrointestinal tract. Thus, the CK7-negative/CK20-positive expression profile has been suggested to be the hallmark of primary colon cancer.^{38,39} However, in our case, the immunohistochemical analysis showed a CK7-positive/CK20-negative expression pattern. Moreover, CDX-2 and SATB2 protein expressions were different from typical CRC patterns. Therefore, metastatic colon cancer with an ovarian origin was initially speculated. Given the high incidence of gynecological tumors in the family, we initially considered an ovarian origin. As a result, the lesion was staged as M1 stage IV (pT4aN2M1) and the patient received an adjuvant chemotherapy regimen of nab-paclitaxel and carboplatin. However, preoperative imaging examinations—including PET-CT—as well as intraoperative observations and post-operative PET-CT results revealed no suspicious ovarian lesions. Therefore, we concluded that it was a primary colon cancer, not secondary to ovarian cancer metastasis.

Although relatively rare, the CK7-positive/CK20-negative immunophenotype of primary colon cancer has been shown in several studies. Bayrak *et al.* observed this expression pattern in 2% of 118 CRC cases.³⁷ In addition, Aldaoud *et al.* performed immunostaining of CK7, CK20, CDX2, and SATB2 on 63 CRC patients and demonstrated an even higher proportion of tumors with “abnormal” expression patterns: CK7 positive in 9.5% cases, CK20 negative in 12.7% cases, CDX2 negative in 9.5% cases, and SATB2 negative in 49.2% cases.⁴⁰ Furthermore, the immunohistochemistry profile of CK7/CK20 was found to be associated with clinicopathological characteristics of CRC. For example, CK7-positive was more common in CRC with an invasive ability and lymph node metastasis, although conflicting results exist.^{41–43} Altogether, the CK7-positive/CK20-negative immunophenotype cannot definitively exclude a colorectal origin.

One possible explanation for this atypical IHC phenotype is the *BRCA1* germline mutation. It is known that *BRCA1*-mutated breast and endometrial cancers often show distinct histological and immunohistochemical profiles compared to their sporadic counterparts.^{44,45} Although less studied in CRC, *BRCA1* mutation carriers may exhibit a predisposition to mucinous, left-sided, and

poorly differentiated tumors.⁴⁶ The deceptive IHC profile observed in this case may thus reflect an underlying *BRCA1*-driven molecular phenotype.

Finally, *BRCA1/2* mutation carriers are known to harbor increased sensitivity to platinum-based regimens and PARPi. Various PARPi, including niraparib, which has been approved by the FDA, is used in treating ovarian, prostate, breast, fallopian, and pancreatic cancers with *BRCA1/2* mutations.^{47,48} The investigations of the PARPi drug for CRC treatment began with veliparib, demonstrating its efficiency in *BRCA1*-deficient colon cancer cells.⁴⁹ While no PARPi has currently been approved by the FDA or NMPA for CRC treatment, several ongoing clinical trials are evaluating their utility in microsatellite stable CRC with *BRCA1* mutations.⁵⁰ CRC cell lines, patient-derived organoids, and patient-derived xenografts were genomically profiled to assess the sensitivity of the cells to PARPi olaparib and the chemotherapeutic agents oxaliplatin and 5-fluorouracil. Most of the cell lines sensitive to PARPi also exhibit cross-sensitivity to oxaliplatin, indicates that oxaliplatin efficacy can be used to identify tumors with a similarity to those carrying germline *BRCA* mutations.⁵¹ Mauri *et al.*⁵² emphasized the therapeutic promise of PARPi in DNA damage response (DDR)-deficient CRC. In our case, the patient with primary colon cancer carrying a *BRCA1* germline mutation showed significant and sustained benefit from niraparib, reinforcing the therapeutic potential of PARPi in this context.

4. Conclusion

This report describes a female CRC patient carrying two germline mutations in *BRCA1* and a family history of ovarian and endometrial cancers. Two mutations of *BRCA1* (c.212+2T>G and c.5123C>T) were detected in all her relatives affected with cancer, along with other healthy individuals tested, suggesting a hereditary pathogenic role underlying multiple cancer types in the family. This case provides real-world evidence for the potential pathogenicity of the newly identified *BRCA1* c.212+2T>G mutation. However, considering that only limited data are currently available, population research is required to assess disease penetrance. This case also emphasizes the importance of molecular testing, especially multi-gene testing in cancer patients with high-risk family histories. The precise identification of gene mutation also helps with personalized treatment decisions, including the choice of targeted drugs. Further, the atypical IHC phenotype observed in this case suggests that *BRCA1* mutations may influence tumor presentation in CRC, warranting further investigation.

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Conflict of interest

Linhan Li was a previous employee of Genetron Health Co., Ltd., Beijing, China. However, the author has not influenced the content of the manuscript. No reference to the author's company is made, but it is declared for full transparency. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Funding acquisition: Ya-rong Guo

Investigation: Bao Chai, Zhi-yong Shi

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Writing – original draft: Bao Chai

Writing – review & editing: Ya-rong Guo, Zhi-yong Shi, Yang Liu

Ethics approval and consent to participate

Informed consent was obtained from the human subjects as per institutional policy.

Consent for publication

Consent for publication was obtained from the human subjects as per institutional policy.

Availability of data

Data are available from the corresponding author upon reasonable request.

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Appendix

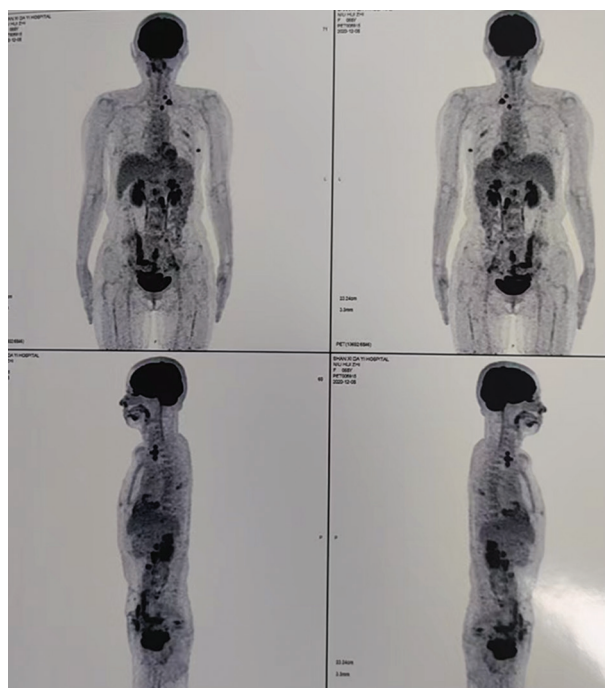


Figure A1. Image of positron emission tomography-computed tomography scan taken in December 2020