

Case Report

Detection of BRCA1 Pathogenic Variant in a 24-Year-Old Endometrial Cancer Patient: Risks of Several Hereditary Tumor Syndromes Assessed Using Germline Multigene Panel Testing

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Keywords

Endometrial cancer · *BRCA1* · Multigene panel testing · Hereditary breast and ovarian · cancer syndrome · Lynch syndrome

Abstract

A 24-year-old woman suspected of Lynch syndrome was found to carry a *BRCA1* pathogenic variant, based on germline multigene panel testing (MGPT). The patient was diagnosed with endometrial carcinoma and underwent modified radical hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and omentectomy at the age of 23. Based on her father's history of colorectal cancer and her history of early onset endometrial cancer, mismatch repair protein immunohistochemistry analysis was performed. However, no loss of expression for mismatch repair proteins was found. Given her family history of ovarian and breast cancers, MGPT was recommended to identify the presence of any hereditary tumor syndromes. This testing revealed a *BRCA1* pathogenic variant (exon13: c.1016delA, p.Lys339ArgfsX2) and

diagnosed as hereditary breast and ovarian cancer syndrome (HBOC). Subsequently, the patient's mother also underwent single-site analysis for this variant, and the same pathogenic variant was detected. The patient and her mother are at high risk of developing *BRCA1*-associated HBOC-related cancers. Based on family history, clinical surveillance is currently underway for this patient and her mother. Currently, MGPT offers the potential for comprehensive genetic cancer risk assessment and may provide a more rational approach for the genetic assessment of those individuals whose personal and family cancer histories do not fit neatly into a single syndrome. This case suggests that if a patient is at high risk for hereditary tumor syndromes, MGPT should be considered to improve disease management strategies in clinical settings.

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Published by S. Karger AG, Basel

Introduction

Women carrying a germline *BRCA1/2* pathogenic variant have an increased risk of developing several malignancies, particularly breast and ovarian/fallopian tube/peritoneal cancers; and it is infrequently reported as other cancers, including endometrial cancer (EC) [1, 2]. Nongenetic and genetic risk factors influence susceptibility to EC development. A family history of EC is associated with an approximate two- to three-fold increase in the risk of developing EC [3]. Several pathogenic germline variants in specific genes are responsible for cancer susceptibility syndromes with an elevated risk of EC [4]. Hereditary EC is associated with hereditary tumor syndromes, i.e., Lynch syndrome (LS), and PTEN hamartoma tumor syndrome/Cowden syndrome, and in a few cases, hereditary breast and ovarian cancer (HBOC) syndrome [4]. LS accounts for 2–6% of all EC cases and is caused by autosomal dominant disorders in DNA mismatch repair (MMR) genes [5]. MMR genes primarily include *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. Functional deletion of MMR genes increases the incidence of colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, small bowel, and urothelial cancers in individuals who harbor pathogenic germline variants [5]. Cowden syndrome is a rare condition resulting from a mutation in the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene, which poses an increased risk of EC [4]. HBOC syndrome is a dominantly inherited autosomal disease that confers predisposition mostly to breast and ovarian cancers. It is characterized by onset at a young age, having more than one synchronous or a metachronous tumor, similarity to bilateral breast cancer, and a family history of first- and second-degree relatives with HBOC-related cancers. The causative genes for HBOC syndrome are known as *BRCA1/2*. Whether *BRCA1/2* pathogenic germline variants also confer an elevated lifetime risk for EC remains elusive. Some studies have reported an increased risk for EC in *BRCA1/2* mutation carriers based on tamoxifen use or country-specific incidence rates [6, 7], whereas contrasting results showing no association have also been found [8]. These conflicting data in previous cohort studies can be attributed to a limited number of EC cases based on small cohort sizes, low mean or median age at enrolment with limited follow-up periods, or absence of outcome validation [6–8]. Recent studies have suggested that, in addition to EC showing serous-like histology, a large group of ECs with an abnormal *p53* signature (one of the four molecularly defined subgroups: *p53*-abnormal [*p53*abn], *POLE*-ultramutated [*POLE*mut], MMR-deficient [*dMMR*], and no specific molecular profile EC) is more common in *BRCA1/2* pathogenic variant carriers [9].

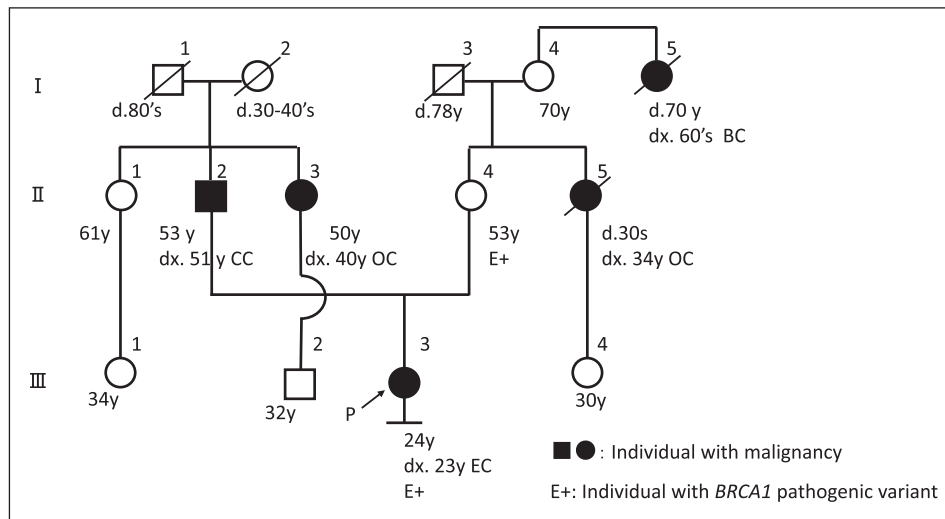


Fig. 1. Family tree of the patient. The patient is indicated with an arrow. d, age at death; dx, age at diagnosis; BC, breast cancer; CRC, colorectal cancer; EC, endometrial cancer; OC, ovarian cancer.

Case Report

A 23-year-old woman with menstrual history was diagnosed with EC through a biopsy performed in her clinician's office. Her height and weight were 169 cm and 76 kg, respectively, and her body mass index was 26.6. This patient was diagnosed as having EC, endometrioid carcinoma grade 3. There was suspicion of peritoneal dissemination by the preoperative computed tomography examination; however, during the operation, no peritoneal dissemination was found. The patient underwent modified radical hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and omentectomy. The final histopathological diagnosis indicated endometrioid carcinoma grade 2, invading less than half of myometrium. No lymph node involvement was confirmed, and she was finally diagnosed with Stage IA (FIGO 2018). Based on clinical and pathological factors, her disease is identified as low risk and can be managed with surgery alone. The patient continues to visit the hospital for routine medical checkups for early detection of EC recurrence. Presently, there is no recurrence of EC.

The patient's family tree is shown in Figure 1. On the maternal side, her grandaunt (I-5) had a history of breast cancer at the age of 60. Her maternal aunt (II-5) had ovarian cancer at the age of 34. Her paternal aunt (II-3) had a history of ovarian cancer by her forties. Furthermore, her father (II-2) had colorectal cancer at the age of 51.

The attending physician suggested hereditary involvement of the patient's EC, and genetic counseling was provided with informed consent at the age of 23. First, LS was suspected based on her history of EC and her paternal family history of colorectal and ovarian cancers. MMR protein immunohistochemistry analysis of her endometrial specimens was performed. The MMR proteins were well expressed in her EC specimen, and the possibility of LS, along with her family history, was ruled out; the genetic factor was still assumed to be linked with carcinogenesis. Therefore, germline multigene panel testing (MGPT; Laboratory Corporation Japan, Tokyo, Japan) was performed (Table 1). A *BRCA1* pathogenic variant (c.1016delA, p. Lys339ArgfsX2) was revealed in her germline at the age of 24. Her mother underwent segregation analysis, and the same pathogenic variant in *BRCA1* was detected (c.1016delA, p. Lys339ArgfsX2).

Table 1. List of 22 genes in panel

APC	MLH1	POLE	BRCA1	POLD1	CDKN2A
ATM	MSH2	PTEN	BRCA2	SMAD4	BMPR1A
BLM	MSH6	TP53	CHEK2	STK11	
CDH1	PMS2	AXIN2	EPCAM	MUTYH (biallelic)	

With genetic counseling to disclose the results, information regarding the future risk of breast and ovarian cancers were explained to the client. As the bilateral ovaries were already resected, risk-reducing mastectomy was recommended and discussed with the patient based on her family history, according to the National Comprehensive Cancer Network Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (v. 1, 2022). Given that a risk-reducing mastectomy was refused by the patient after counseling at the time, an annual breast magnetic resonance imaging screening with contrast or mammogram examination was recommended. At the first examination for breast surveillance, there was no malignant breast disease. Currently, the patient is 26 years old and has not undergone a risk-reducing mastectomy. Instead, she is under surveillance for breast cancer. The option of prophylactic resection of the mammarys (by risk-reducing mastectomy) will be considered. Genetic counseling was also considered for her family members. Her mother has already been diagnosed with HBOC and is under surveillance for breast and ovarian cancers.

Discussion

In this study, a *BRCA1* pathogenic variant was detected in a patient with early onset EC. The *BRCA1* variant (c.1016delA, p. Lys339ArgfsX2) was identified as pathogenic, based on previous findings [10–12]. This variant has been reported in a Chinese patient with breast cancer [12] and HBOC [11]. Upon reviewing her family tree, we found that her grandaunt (I-5) had a history of breast cancer in her sixties, one maternal aunt (II-5) had a history of ovarian cancer at the age of 34, one paternal aunt (II-3) had a history of ovarian cancer at the age of 40, and her father (II-2) had colorectal cancer at the age of 51. As breast and ovarian cancers are both related to HBOC, the patient may have inherited the *BRCA1* variant from her parents. Given that her mother has the same pathogenic variant, the maternal origin of mutation was confirmed.

Additional examination of her other family members should be considered to clarify hereditary tumor involvement; segregation analysis is recommended. An important clinical consideration in this patient was that the bilateral ovaries and fallopian tubes were resected. However, the fallopian tubes were not pathologically examined, in accordance with the modification of standard fallopian tube dissection protocols (SEE-FIM protocol), because the operation was performed before genetic diagnosis. Following the *BRCA1* pathogenic variant diagnosis, pathological examination of the fallopian tubes based on the SEE-FIM protocol was recommended. However, resident nontumor tissue was not retained. As total modified radical hysterectomy and bilateral salpingectomy were performed to treat the EC, the risk of ovarian cancer related to the *BRCA1* pathogenic variant decreased. However, the risk of undetected (occult) ovarian or tubal neoplasia and other cancers still exists. If HBOC is suspected, the typical protocol involves testing for *BRCA1/2* first, followed by additional genes in sequence, only if the patient meets the accepted criteria for various other genetic syndromes. However, the National Comprehensive Cancer Network (NCCN) Guidelines were drastically changed to recommend comprehensive MGPT in 2020. This patient did not meet the Testing Criteria

for High-Penetrance Breast and Ovarian Cancer Susceptibility Genes according to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, as she had no history of breast or ovarian cancers. Therefore, it was difficult to evaluate the risk of HBOC in this patient based on personal and family histories alone. Thus, MGPT may contribute to disease management in clinical settings based on results that cannot be obtained by either conventional risk assessment methods or single-gene analysis, according to the NCCN Guidelines [13]. Previous studies have indicated that MGPT can increase the detection rate of any pathogenic variant, including non-*BRCA1/2* variants such as LS genes, in patients with suspected HBOC, which can alter clinical management strategies for cancers [14].

Here, we suggest that MGPT may be useful for improving clinical management strategies for patients primarily suspected to have LS and not HBOC. However, several factors should be considered when performing MGPT. The results obtained for the targeted genes or variant annotations may differ among commercially available tests. The possibility of identifying variants of uncertain significance or variants in genes that are not clinically relevant should also be considered. Professionals who provide genetic counseling should be familiar with up-to-date information regarding the aforementioned issues. A large cohort study confirmed that the highest risk has been found in *BRCA1* pathogenic variant carriers (10- to 13-fold greater than wild-type *BRCA1*) [15]. However, *BRCA2* pathogenic variant carriers also show a five-fold-increased risk compared to that of the general population. By contrast, endometrioid EC risk is only increased in *BRCA1* pathogenic variant carriers (two- to three-fold) [15]. In this case, the patient had a *BRCA1* pathogenic variant, and the EC histology subtype was endometrioid carcinoma. Therefore, it is possible that the *BRCA1* variant affected the etiology of EC even though this patient had nongenetic clinical features of EC, such as obesity. Although nulliparity and obesity are risk factors, the mechanism underlying the development of EC at her age remains unknown.

Conclusion

We present a case in which MGPT revealed a *BRCA1* pathogenic variant in a patient who had been suspected of LS rather than HBOC. Clinicians should evaluate the detailed history of patients and their families, particularly when planning a surgery, and should carefully select an appropriate genetic testing tool that can confirm or alter the choice of the clinical management strategy.

Acknowledgment

We would like to thank Editage (www.editage.com) for English language editing.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local guidelines. Written informed consent was obtained from the patient for the publication of this case report.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

Funding Sources

No funding was obtained from private or public sectors for this research.

Author Contributions

Xiaofei Wang designed this study. Dr. Makiko Omi and Eri Nakashima were the patient's oncologists. Keika Kaneko, Hiromi Arakawa, Eri Habano, Dr. Hiroshi Kawachi, Dr. Akiko Tonooka, Dr. Kohei Omatsu, Dr. Hidetaka Nomura, Dr. Mayu Yunokawa, Dr. Hiroyuki Kanao, Dr. Shunji Takahashi, and Dr. Takeshi Nakajima reviewed the literature. Dr. Arisa Ueki was responsible for the revision of the manuscript. All authors contributed to data acquisition and analysis. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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