A new pathogenic mutation of the BRCA1 gene in a patient with ovarian cancer

A case report

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Abstract

Rationale: The breast cancer susceptibility gene (BRCA) is an important tumor suppressor gene and tumor susceptibility gene. Germ line BRCA1/2 mutations significantly increase the risk of breast cancer and other cancers in women.

Patient concerns: A 48-year-old woman was diagnosed with breast cancer at the age of 42 and subsequently diagnosed with ovarian cancer at the age of 48. Her sister had a history of breast cancer and her mother died from ovarian cancer.

Diagnoses: The patient has a family history of tumors. BRCA1/2 mutations was proved in this family members.

Interventions: Sanger sequencing was used to evaluate the BRCA1/2 gene status of the patient and her sister to identify the genetic mutation sites.

Outcomes: They had the same genetic mutation, namely, the c.3487_3488insA (p.Thr1163AsnfsX2) mutation in the BRCA1 gene, which is a novel mutation.

Lessons: This novel mutation may be a new pathogenic mutation of the BRCA1 gene. Its relationship to breast and ovarian cancers needs to be further verified in more patient cases. Moreover, mutant protein functions in both cell and animal models are also needed.

Abbreviations: BRCA = breast cancer susceptibility gene, CT = computed tomography.

Keywords: BRCA, mutation, ovarian cancer, pathogenic

1. Introduction

Ovarian cancer is one of the common malignant tumors of the female reproductive system, with an incidence rate that ranks it as the third most common gynecologic cancer behind cervical and uterine cancers. However, ovarian cancer is the gynecologic malignancy with the highest mortality rate. Clarifying the methods of timely detection, diagnosis, and prevention of ovarian cancer to decrease its incidence and mortality rate has been the key goal of gynecologic oncolgists for decades. With the development of precision medicine, mutations in the breast cancer susceptibility genes (BRCAs) including BRCA1 and BRCA2, have come to be known to be related to the pathogenesis of hereditary ovarian and breast cancer. Approximately 30% of hereditary ovarian and/or breast cancer occurrences are associated with BRCA1/2 gene mutations\textsuperscript{[1,2].} To date, there are thousands of mutation positions that have been discovered in the BRCA1/2 genes. In the general population, the risk of breast cancer is about 10%, and for ovarian cancer it is about 1%, whereas the risk of breast or ovarian cancer in women with BRCA missense mutations exceeds 80\textsuperscript{%}\textsuperscript{[1,2].} Therefore, it is necessary to conduct early screening and clinical interventions in these high-risk populations. Herein, we report the case of a woman diagnosed with ovarian and breast cancer, with a mutation in the BRCA1 gene that may be a new pathogenic mutation.

2. Case report

A 48-year-old woman, gravida 3, para 1, had been postmenopausal for 2 years. At the age of 42 she underwent a left breast radical mastectomy due to breast cancer on the left side, without postoperative adjuvant therapy. She maintained regular outpatient follow-ups. In 2016, she presented and was admitted to our hospital due to complaints of “bloating for more than 1 month and progressive worsening.” Transvaginal color Doppler ultrasound detected a 16.1 x 11.4 x 15.6 cm mixed cystic and solid pelvic mass with an irregular shape and a blood flow signal resistive index = 0.64 (Fig. 1A). An abdomen and pelvis computed tomography (CT) scan revealed irregularly shaped...
cystic and solid masses in the bilateral ovaries and fallopian tubes. The left mass measured approximately 8.1 × 5.2 × 15.6 cm and was predominantly solid. The right mass measured approximately 10.3 × 8.2 × 9.8 cm and was predominantly cystic (Fig. 1B). Enhanced CT scanning demonstrated uneven enhancement, with an “ovarian vascular pedicle” on each side (Fig. 1C). The serum cancer antigen 125 level was 3952.6 U/mL. The patient underwent 3 separate paracentesis procedures, with a
total of 6200 mL of light yellow ascites removed. The ascitic fluid was positive for tumor cells. At that time, a malignant tumor was suspected, possibly originating from the reproductive system. On the recto-vaginal and abdominal examinations, huge cystic-solid masses in the pelvis and abdomen, suspected severe intestinal adhesions, and extensive hard nodular lesions on the sacroiliac ligaments were detected. Three gynecologic oncology specialists and imaging specialists evaluated the CT scan images and the findings scored 10(10/23) according to the Bristow standard, which indicated that the predictive index score ≥ 4 would be helpful to more accurately identify patients with advanced epithelial ovarian carcinoma that were unlikely to undergo optimal primary cytoreductive surgery. They suggested that such patients would not achieve satisfactory results from tumor reduction surgery, and instead, preoperative adjuvant chemotherapy should be recommended. For our patient, a preoperative paclitaxel–cisplatin combined regimen (paclitaxel 175 mg/m² intravenous guttae (ivgtt) + cisplatin 75 mg/m² ivgtt, at intervals of 3 weeks) was administered for a total of 3 courses. In late 2016, she underwent a laparoscopic hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymph node dissection. The surgical outcome was satisfactory with no residual cancer foci. The postoperative biopsy results demonstrated high-grade serous adenocarcinoma of the bilateral ovaries that also involved the bilateral fallopian tubes and bilateral pelvic walls, but there was no lymph node involvement (Fig. 2). Subsequently, the patient received a postoperative paclitaxel–cisplatin regimen that included carboplatin (paclitaxel 175 mg/m² ivgtt + cisplatin 75 mg/m² ivgtt, carboplatin 400 mg/m² ivgtt, at intervals of 3 weeks) for 8 courses. The chemotherapy was completed in mid-2017 and the patient has continued close follow-up to this point.

During chemotherapy she suffered from severe vomiting, fatigue, and moderate bone marrow suppression. Her symptoms were significantly relieved after symptomatic support treatment. Her serum cancer antigen 125 decreased significantly to 10 U/mL after 3 cycles of preoperative chemotherapy, and it declined progressively during the postoperative chemotherapy finally reaching 5.1 U/mL at the end of the chemotherapy course. Follow-up lung and pelvic CT scans were performed after 3 and 8 courses of postoperative chemotherapy, respectively. Both results showed that the patient was in a state of complete remission (CR).

After 3 courses of postoperative chemotherapy, our patient’s blood was subjected to BRCA testing (Sanger sequencing, Shenzhen BGI Clinical Laboratory Center). The results demonstrated a frame shift mutation of the BRCA1 gene c.3487_3488insA (p.Thr1163AsnfsX2). This patient had a family history of malignancy, as her sister was diagnosed with breast cancer at the age of 41 (Fig. 3). Further Sanger sequencing confirmed that the sister had the same BRCA1 gene mutation as our patient. In mid-2016, the sister underwent laparoscopic hysterectomy with bilateral salpingo-oophorectomy at our hospital. No malignant tumors were found on biopsy. She was discharged 2 days later and had all normal follow-up evaluations. Their mother was diagnosed with ovarian cancer at the age of 57, which was her ultimate cause of death, and their father has gastric cancer (Fig. 3).

3. Discussion

BRCA mutations in the class I category (risk of breast, ovarian, and other cancers in women ≥ 20%) are likely to have higher risk, and these patients are recommended for prophylactic surgery. Preoperative adjuvant chemotherapy should be considered for patients with high-risk ovarian cancer as a potential alternative to prophylactic surgery. Among patients with high-risk ovarian cancer, many will have advanced disease at initial diagnosis because of the advanced-stage disease at initial diagnosis. The current study included those patients with advanced-stage disease at initial diagnosis. Preoperative adjuvant chemotherapy should be recommended. For our patient, a preoperative paclitaxel–cisplatin combined regimen (paclitaxel 175 mg/m² ivgtt + cisplatin 75 mg/m² ivgtt, at intervals of 3 weeks) for 8 courses. The chemotherapy was completed in mid-2017 and the patient has continued close follow-up to this point.

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BRCA mutation classification is based on the published data in Europe and the United States. In 2017, for the first time and based on a large sample, Wu et al reported that the BRCA mutation rate in patients with ovarian cancer in China was 27.8%, of which 20.8% were BRCA1 mutations and 7.6% were BRCA2 mutations. However, China has not yet established a large database of gene mutations. Whether the mutation sites are different from those in the European and American populations needs to be determined from clinical and basic research combined with patient and family histories. Continuing discoveries and studies of new pathogenic gene mutation sites and types could provide important guidance for screening, early diagnosis, intervention, and treatment of ovarian cancer in China. In this report, BRCA gene tests found a BRCA1 gene frame shift mutation c.3487_3488insA (p.Thr 1163AsnfsX2) that resulted in an encoding length of 1163 amino acids, which represented a truncated polypeptide chain since the normal BRCA1 gene encodes 1863 amino acids. Until now, there has been no report on the functional studies and clinical significance of this mutation, and its frequency is 0 in the One Thousand Genomes Project. This mutation is suspected to be pathogenic. Moreover, our ovarian cancer patient had a history of breast cancer and a significant family history of malignant tumors. Therefore, clinically it is recommended to escalate the frame shift mutation of the BRCA1 gene c.3487_3488insA (p. Thr1163AsnfsX2) to a pathogenic grade. This is a newly discovered pathogenic mutation in the Chinese population and imparts great value to the screening and early diagnosis of ovarian/breast cancer. However, the new mutation has been identified only in 2 cases in this family, because the patient’s mother died of ovarian cancer many years ago, and therefore, testing of the mother could not be performed. In addition, the protein function associated with this mutation has yet to be completed.

4. Conclusion

The c.3487_3488insA (p.Thr1163AsnfsX2) BRCA1 mutation may be a new pathogenic mutation in the BRCA1 gene. Its association with breast and ovarian cancers needs to be further verified through more case studies. Moreover, mutant protein function research in both human cells and animal models are also needed.

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