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Case Report

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Genetic Insights into Endometrial Cancer: A Case Report on BRCA2 Pathogenic Variant

Asieh Shakib[1], Ramin Ajami[2*], Amineh Sadat Vaghefi[3]

Abstract

The most common female reproductive system cancers include cervical, endometrial, and ovarian cancers [1]. According to GLOBOCAN 2018, more than 1 million women (approximately 1,250,000) are affected by these cancers worldwide [2]. Endometrial cancer (EC) ranks as the fourth most common cancer in women and is the predominant gynecological malignancy in the US [12], with its incidence steadily rising. About 5% of uterine cancers are caused by a germline mutation, the majority of which are attributed to defects in mismatch repair genes, commonly associated with Lynch syndrome. Approximately 75–80% of endometrial cancers (ECs) are endometrioid adenocarcinomas. Curative treatment in this setting involves a hysterectomy resulting in the removal of the ovaries and fallopian tubes.

Pathogenic variants in BRCA1 and BRCA2 genes cause hereditary breast and ovarian cancer (HBOC) syndrome, associated with an increased lifetime risk of breast, ovarian, prostate, and pancreatic cancers [6, 7]. Endometrial cancers are not formally associated with HBOC but have been reported in HBOC patients [8]. EC prevalence in BRCA1/2 carriers is not well established, but according to the literature, most cases are related to BRCA1. Here, we discuss a particular EC patient harboring a BRCA2 mutation.

Keywords: Genetic; Endometrial cancer; BRCA2; Pathogenic variants; Lynch syndrome.

Background

Endometrial cancer (EC) ranks as the fourth most common cancer in women and is the predominant gynecologic malignancy in the US [12], with its incidence steadily rising. EC is traditionally categorized into two primary types: Type I, which constitutes about 80% of cases and has a favorable prognosis, and Type II, accounting for 10–20% of cases with a poorer prognosis [14]. While EC typically develops in post-menopausal women, a significant 20–25% of cases are diagnosed before menopause [13]. Well-characterized risk factors include menopausal status, obesity, diabetes, hypertension, and unopposed oestrogen [15]. Notably, 2%–5% of EC cases are linked to familial factors, associated with specific germline mutations. Type 1 endometrial cancer is often linked to excess oestrogen, typically stemming from conditions such as obesity, oestrogen therapy without progesterone, early onset of menstruation, late onset of menopause, and polycystic ovarian syndrome. Conversely, type 2 endometrial cancer is not strongly influenced by excess oestrogen and is commonly associated with factors such as older age, thinness, hypertension, and a history of breast

Affiliation:

[1]Department of Internal Medicine, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Oncology, Royal Free Hospital, London, United Kingdom

[3]Omid Genetic Laboratory, Tehran, Iran

***Corresponding author:**
Ramin Ajami, Department of Oncology, Royal Free Hospital, London, United Kingdom

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or ovarian cancer. Understanding these distinct risk factors for each type of endometrial cancer is crucial in developing targeted prevention and screening strategies for individuals at higher risk. The primary curative option for early-stage EC is hysterectomy and bilateral salpingo- oophorectomy, which aids in staging and tailoring adjuvant treatment for high-risk patients [16]. Understanding the genetic basis of EC has provided valuable insights into the disease's biology, revealing molecular alterations that may be targeted for therapy.

Clinical Report

A 47-year-old female was evaluated for abnormal vaginal bleeding in February 2016 and underwent a total abdominal hysterectomy due to severe bleeding. She had a history of obesity, had never used birth control pills or any other hormonal treatments, and had hypertension. Her obstetric history revealed two deliveries (one normal vaginal and one caesarean section), with breastfeeding after each. Additionally, her mother passed away at 60 years old due to liver cancer, and her aunt passed away at 65 years old due to a brain tumour. Pathology of hysterectomy samples confirmed well-differentiated endometrioid adenocarcinoma, with perineural and lymph node involvement (right and left iliac and obturator lymph nodes) at FIGO stage III C1. She received six cycles of chemotherapy with paclitaxel and carboplatin from March, followed by 18 sessions of external and 4 sessions of internal radiotherapy until September 2016. There were no issues during follow-up until November 2020, when the patient presented with a chest wall mass, with CT scans revealing metastases in the lung, soft tissues, bone, and vertebral bodies. A PET scan revealed FDG-avid metastatic disease, including a soft tissue tumour within the chest wall with invasion to the 8th rib, a left upper lobe pulmonary nodule, a left posterior pleural lesion, a few thoracic and abdominal lymph nodes, and a few right paracaecal peritoneal lesions.

A second opinion on her previous pathology report of the uterine sample confirmed well- differentiated endometrial adenocarcinoma, endometrioid type, invading the myometrium. Subsequently, the patient underwent chemotherapy with a gemcitabine and docetaxel regimen in November 2020. During surgery the following month, the chest wall mass was resected, and a sample of the pulmonary nodule was taken. The biopsy reports indicated a poorly differentiated adenocarcinoma with extensive necrosis and invasion of bone and muscle tissue for both the chest wall mass and the wedge resection biopsy of the left lung. Chemotherapy continued from January to April 2021 with carboplatin and doxorubicin. In May 2021, a CT scan was performed to check the treatment response, revealing a calcified mass in the right upper lobe next to the chest wall, multiple lytic lesions in the ribs and lumbar vertebrae (likely due to metastasis), and a chest wall mass with a cystic component at the level of the left hemidiaphragm, involving and encasing the ribs at this level. Additionally, two paracaecal mesenteric nodules up to 13 mm were seen (most likely due to metastasis). Consequently, palliative treatment was recommended due to the metastatic conditions of the disease. For follow-up in April 2022, a CT scan showed multiple pulmonary and pleural metastases with chest wall involvement, adenopathic mass at the infrarenal level of the pre-aortic region, omental mass (peritoneal metastasis) at the right paraumbilical space, and two smaller masses at the right lower quadrant and periumbilical region. In August 2022, a germline mutation was examined to investigate the possibility of targeted treatment. The sample was positive for a germline pathogenic mutation, p.L1152* [c.3455T>G, p. (Leu1152Ter)], in the BRCA2 gene, related to Hereditary Breast and Ovarian Cancer Syndrome as evaluated by NGS and confirmed by Sanger sequencing. The loss-of- function pathogenic BRCA2 mutation suggests the potential benefit of poly ADP-ribose polymerase inhibitors (PARP inhibitors) (Olaparib, Rucaparib, Niraparib, and Talazoparib) as well as platinum-based chemotherapy drugs (Carboplatin, Cisplatin, Oxaliplatin). According to the germline pathogenic mutation, targeted therapy with PARP inhibitors was scheduled for her, and no sign of disease progression was noticed in the follow-up PET scan.

Discussion

It was highlighted that since the most relevant mutation in EC occurs in DNA mismatch repair genes, microsatellite instability (MSI) testing is typically requested for EC patients. In this patient, MSI status was intact, but a germline pathogenic variant in the BRCA2 gene was identified, a gene usually associated with individuals with a family history of breast and/or ovarian cancer. The allele frequency of this variant in the general population is 3.98×10^{-11} (11). BRCA1/2 pathogenic mutations are associated with an increased risk of serous uterine cancer. [4] reported that based on their study of 438 BRCA1 mutation carriers and 390 BRCA2 mutation carriers, three and two incident cases of uterine cancer were reported, respectively, compared to 1.04 expected and 0.99 expected. All cases were of the endometrioid subtype, International Federation of Gynaecology and Obstetrics stage I–II disease. [5], in their meta-analysis, showed pooled prevalence rates of EC in BRCA1/2 mutation carriers were 0.59%. The EC prevalence was 0.62% in BRCA1 mutation carriers and 0.47% in BRCA2 mutation carriers, with a relative risk of 1.18. Most studies in this meta-analysis suggest a slightly increased risk of EC in BRCA mutation carriers, mainly for BRCA1. This case represents a rare association of a germline BRCA2 mutation in endometrial cancer. To the best of our knowledge, this is the first reported case in Iran. Previous studies suggest that hereditary breast and ovarian cancer (HBOC) should be suspected in individuals with a

personal or family history of BRCA1 or BRCA2 pathogenic variants, such as in this patient who harboured a BRCA2 mutation. Due to this genetic finding, genetic counselling has been arranged for the patient and her family members to help guide preventive care.

Conclusion

In conclusion, this case serves as a compelling illustration of the intersection between genetic insights, clinical management, and the potential for tailored targeted therapies in the context of endometrial cancer. Notably, the identification of a germline pathogenic mutation in the BRCA2 gene has paved the way for targeted therapy with PARP inhibitors, marking a significant advancement in personalized treatment strategies for endometrial cancer patients with specific genetic profiles. The rarity of this germline mutation in the context of endometrial cancer, especially in the Iranian population, underscores the significance of this case as a unique contribution to the understanding of endometrial cancer genetics. Furthermore, this case highlights the importance of genetic counselling for the patient and her family members to guide preventive measures, informed decision- making, and assessing familial cancer risk.

Authors' Contributions

ASV and RA designed the study. ASH reviewed the article. AS collected the data, and AS and RA wrote the manuscript. AV performed the editing.

Data availability

The data supporting the findings of this study are available upon request.

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