

Identifying Lynch Syndrome in Two Families with Classical Hereditary Breast and Ovarian Cancer Syndrome Phenotype: A Case Report

Salha Bujassoum^{1*}, Reem Alsulaiman¹, Hind Elmalik¹, Kulsom Junejo², Ahmed Mahfouz³ and Hanan Farghaly⁴

¹Department of Medical Oncology, National Centre for Cancer Care and Research, Doha, Qatar

²Department of Breast surgery, Hamad General Hospital, Doha, Qatar

³Department of Radiology, Hamad General Hospital, Doha, Qatar

⁴Department of Histopathology, Hamad General Hospital, Doha, Qatar

*Corresponding author: Salha Bujassoum, Senior Consultant Medical Oncology/Hematology, Lead of Hereditary Cancer Program, Department of Medical Oncology, National Centre of Cancer Care and Research, Doha, Qatar, Tel: +97444397800; E-mail: sbujassoum@hamad.qa

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Abstract

Introduction: Although the consideration of breast cancer as spectrum of Lynch syndrome has not been clearly delineated, multigene panel studies suggest that individuals with Lynch syndrome may have an increased risk for breast cancer and may present with a Hereditary Breast and Ovarian Cancer Syndrome (HBOC) phenotype. In this case report, we present two cases who presented to the genetics clinic with classical HBOC phenotype and who didn't meet Lynch syndrome testing criteria and were later found to be negative for *BRCA* mutations but positive for Lynch syndrome through multigene panel testing.

Case 1: A 57-years-old French-Canadian female with high grade serous ovarian cancer with intact *MMR* nuclear expression and family history of young onset breast cancer was referred to the genetics clinic to be evaluated for HBOC. The patient was later found to be negative for *BRCA* mutations but positive for a pathogenic mutation in the *MSH2* gene through multigene panel.

Case 2: A 59-years-old unaffected patient of Ashkenazi Jewish descent with bilateral fibrocystic breast who presented to our clinic with family history of young onset breast and gastric cancers. Through multi-gene panel, the patient was found to be negative for *BRCA* genes mutations but positive for a pathogenic mutation in the *PMS2* gene.

Discussion and Conclusion: This report draws the attention on the importance of multigene panels in identifying individuals with Lynch syndrome who present with HBOC like phenotype. In addition, it suggests that the current Lynch syndrome diagnostic criteria's may not be sufficiently sensitive in identifying *MMR* mutations in HBOC like families who might miss the opportunity from being identified and benefit from risk reducing strategies, targeted therapies and reproductive options. We therefore suggest a re-consideration of the available Lynch syndrome testing criteria's and we suggest that *MMR* testing to be considered in families with breast and ovarian cancer and HBOC like phenotype.

Keywords: Lynch syndrome; Mismatch repair genes; HBOC; *BRCA1*; *BRCA2*

Introduction

Hereditary Breast and Ovarian Cancer Syndrome (HBOC) are the most common cause of hereditary forms of both breast and ovarian cancers that results due to mutations in the *BRCA1* and *BRCA2* genes [1]. It is known that hereditary breast and ovarian cancer syndrome predisposes females to approximately 85% lifetime risk of breast cancer and up to 60% lifetime risk for ovarian cancer in addition to predisposing men to breast and prostate cancers [1]. Families with hereditary breast and ovarian cancer syndrome are often characterized by early onset breast cancer, often with triple negative histopathology, bilateral breast cancer, ovarian cancer that is often of high grade serous histopathology in addition to male breast and prostate cancers. In addition, HBOC families can sometimes present with pancreatic cancer and melanoma [2-4]. Identifying high risk families for HBOC is

crucial in order to offer them risk reducing strategies, targeted therapies and reproductive options and multiple professional organizations such as National Comprehensive Cancer network (NCCN) have set testing criteria's in place to identify high risk families for HBOC and other hereditary cancer syndromes [5]. However, not all families that meet the criteria for HBOC have a causative mutation within the *BRCA* genes. This had led to the introduction of multi-gene panels which are efficient, cost-effective and have helped in the identification of the causative genes in multiple *BRCA* negative high-risk families [5].

Lynch syndrome, previously referred as hereditary non-polyposis colorectal cancer (HNPCC), is the most common cause of hereditary colon cancer and accounts for 1-3% of all colorectal cancer cases. Lynch syndrome is inherited in an autosomal dominant manner and is caused by mutations in the mismatch repair (*MMR*) genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). 6 In addition, Lynch syndrome can be caused by germline deletions of *EPCAM* gene and such deletions lead

to epigenetic inactivation and silencing of its neighboring gene *MSH2* [6].

Lynch syndrome is known to predispose individuals to colorectal cancer with approximately up to 82% life time risk, 60% for endometrial cancer and about 12% risk for ovarian cancer [3]. In addition, individuals with Lynch syndrome can be at increased risk for hepatobiliary tract, urinary tract, brain, and skin cancers [7]. Germline mutations in the *MLH1* and *MSH2* genes are the most common and account for about 80-90% of Lynch syndrome cases followed by *MSH6* and *PMS2* [7-10]. It is known that mutations in the *MLH1* and *MSH2* genes are significantly associated with higher risk of colorectal cancer than other Lynch syndrome genes. On the other hand, mutations in the *MSH6* gene is significantly correlated with higher risk of endometrial cancer, while, extracolonic cancers including ovarian cancer is often associated with mutations in the *MSH2* gene.

Although the consideration of breast cancer as spectrum of Lynch syndrome has not been clearly delineated, several studies have shown a significant increased risk for breast cancer in individuals with Lynch syndrome reaching up to 22% cumulative life time risk [6,7]. While other studies have found a significant genotype-phenotype correlation and a higher life time risk for breast cancer associated specifically with *MSH6* and *PMS2* genes [8]. A recent study showed that *MSH6* and *PMS2* gene mutations are associated with increased risk of breast cancer with life time risk being between 31.1% and 37.7% [8]. and the study authors suggested that testing for those genes should be considered in individuals with personal or family history of breast cancer [8]. Another study based on a Canadian familial cancer registry have found that *MSH2* was the most common identified mismatch repair gene in the cohort and that mutation carriers have a significantly increased risk for breast cancer reaching up to 22% compared to the life time risk in the general Canadian female population [9]. Interestingly and in another study, it was shown that several families especially those harboring mutations within the *MSH6* and *PMS2* genes may present with a hereditary breast and ovarian cancer syndrome (HBOC) phenotype rather than the Lynch syndrome phenotype suggesting that the current Lynch syndrome testing criteria's may not be sufficiently sensitive to identify those high-risk families [10].

Case Report

In this case report, we present two cases with classical HBOC phenotype because of personal and/or family histories who were later found to be negative for *BRCA* mutations but positive for Lynch syndrome through multi-gene panel testing.

Case 1

A 57-years-old French-Canadian female with no significant past medical history and with family history of breast cancer presented to the oncology clinic with three weeks history of progressive abdominal distension and found to have clinically and radiologically massive intra-abdominal ascites peritoneal carcinomatosis and enlarged ovaries suggestive of bilateral primary ovarian neoplasm (Figure 1).

Laparoscopy revealed massive ascites, multiple abdominal wall lesions, omental cake, pelvic wall lesions and bulky abnormal looking ovaries. Omentum biopsy showed "poorly differentiated carcinoma" and IHC is consistent with "high grade serous (HGS) carcinoma". Staging work up confirms FIGO IIIC and CA125 was 3339 u/ml.

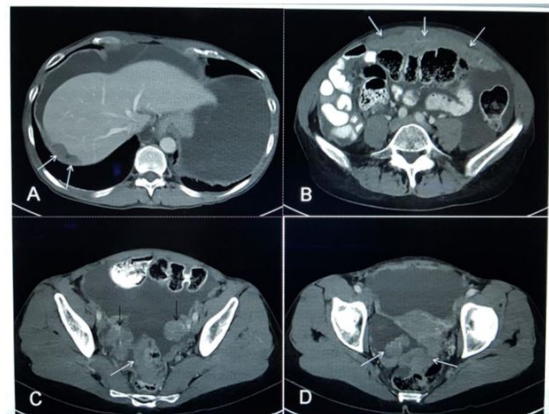


Figure 1: Contrast-enhanced CT of the abdomen and pelvis demonstrates bilateral ovarian solid masses (black arrows) and peritoneal metastases (white arrows) at the surface of the liver, omentum (omental cake) over the surface of the rectum and at the pelvic peritoneal recesses.

Treatment and progress: The patient was started on neoadjuvant chemotherapy (NAC) Taxol and Carboplatin three cycles patient tolerate treatment without major complications and had good clinical response and CA 125 improved response of 332 u/ml. The patient was later underwent interval debulking surgery (IDS), total hysterectomy with bilateral salpingoophorectomy and omentectomy (No Lymph node dissection) with R1 resection. Histopathology treatment response was 10% to 15% pT3c Nx. The patient then received more adjuvant chemotherapy 3 cycles of same protocol in addition to Bevacizumab (Avastin) Q 21 days (modified dose) for the aggressive suboptimal debulking disease.

Clinical follow-up: The patient was later assessed, and she was clinically well with stable disease and with good quality of life and her tumor markers plateaued at around 50-60 u/ml. Because of the patient's personal diagnosis of high grade serous ovarian cancer and her reported family history of young onset breast cancer, she was referred to the genetics clinic at our institution to be evaluated for hereditary breast and ovarian cancer syndrome and to be offered *BRCA* testing for the possible introduction of Olaparib (PARP inhibitor) in the course of her treatment if she progresses and in order to help her family members by pursuing risk reducing strategies if she was found to be positive.

Genetic counseling: The patient was seen at the genetics clinic and was assessed by a board-certified genetic counselor. As can be seen in Figure 2, the patient reported family history of young onset breast cancer in her mother at the age of 32 years who passed away at her 50's. The patient reported a French-Canadian ethnicity. The rest of the patient's family history is unremarkable for any birth defects, consanguinity or any other genetic diseases.

Given the patient's diagnosis of high grade serous ovarian cancer and her reported family history of young onset breast cancer in addition to her French-Canadian ethnicity, hereditary breast and ovarian cancer syndrome was on the top list of our differential diagnoses and the patient was eligible for *BRCA* testing based on the international and on our local testing criteria's. Due to the availability of multigene panels and the reported literatures on other known genes

associated with hereditary ovarian cancer that the patient might be at risk for, the patient was counseled and offered *BRCA* testing as part of the breast/ovarian cancer panel to rule out hereditary ovarian cancer. The panel consisted of twenty genes implicated in hereditary breast and ovarian cancers including *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *FANCC*, *FANCD1*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *TP53*, *XRCC2*.

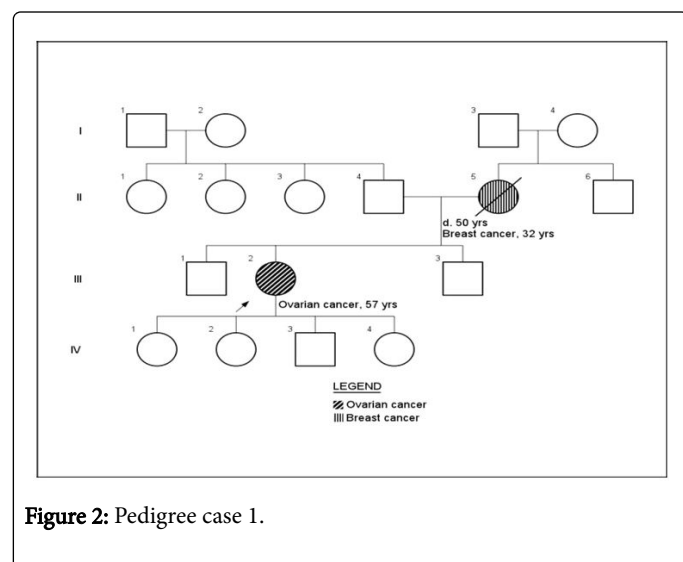


Figure 2: Pedigree case 1.

Three weeks later, the multigene panel results came back and showed no pathogenic mutations or variants in the *BRCA* genes, however, it revealed a heterozygous pathogenic mutation in the *MSH2* gene c.2680dupA (p. Met894AsnfsX5). This duplication of one nucleotide in *MSH2* is denoted c.2680dupA at the cDNA level and p. Met894AsnfsX5 (M894NfsX5) at the protein level. The duplication causes a frameshift which changes a Methionine to an Asparagine at codon 894 and creates a premature stop codon at position 5 of the new reading frame. This variant is predicted to cause loss of normal protein function through protein truncation. Therefore, this mutation is classified as pathogenic and this in turn confirms the diagnosis of Lynch syndrome in the patient.

Since that the patient has metastatic disease, high risk surveillance for both colon and breast cancers are going to be covered through her staging immunohistochemistry workup.

Immunohistochemical staining of MMR versus germline results: We were then interested to explore whether immunohistochemical staining (IHC) on the patient's ovarian cancer tissue would show loss of *MSH2* protein expression or loss of any of the other *MMR* protein nuclear expression. Therefore, histopathology was contacted and IHC for *MMR* was performed on the available ovarian cancer tissue blocks. Unexpectedly, the results of the IHC showed intact nuclear expression of the four *MMR* genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*) as shown in Figure 3.

Case 2

A 59-years-old American unaffected female of Eastern European descent was referred to the breast surgeon due to having bilateral fibrocystic mastopathy of the breast. The patient has history of left breast cystic lesion which was aspirated and showed atypical cells and history of right breast biopsy which was benign. The patient has history of total hysterectomy and bilateral salpingo-oophorectomy

(TAH-BSO) due to post-menopausal bleeding with endometrial hyperplasia.

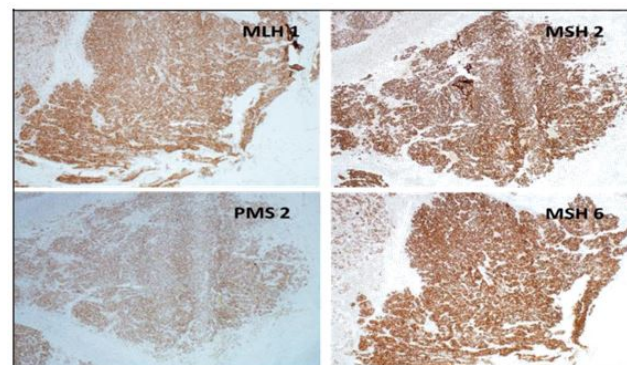


Figure 3: Intact MMR nuclear expression on ovarian cancer tissue.

The patient had been following with the breast surgeon due to her fibrocystic disease of the breast. The patient was later referred to the genetics clinic to be evaluated for hereditary breast and ovarian cancer syndrome due to her reported family history of young onset breast cancer.

Genetic counseling: A three-generation pedigree was taken which revealed family history of old onset breast cancer in the patient's mother at age 90 and young onset of breast cancer in her half-sister from maternal side at her 30's. Family history also revealed a maternal aunt who was diagnosed with gastric cancer at her 50's (Figure 4). Most importantly, the patient reported an Eastern European Ashkenazi Jewish ancestry from her maternal side.

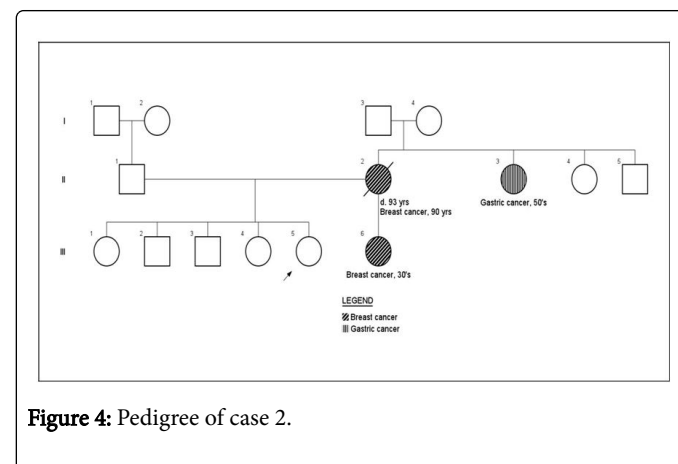


Figure 4: Pedigree of case 2.

Looking at the family history of breast and gastric cancers in addition to the reported Ashkenazi Jewish ancestry, the patient was considered at significantly increased risk for hereditary breast and ovarian cancer syndrome. The patient was offered *BRCA* testing as part of a panel which consisted of twenty genes implicated in hereditary breast and ovarian cancers as mentioned in the first case.

Three weeks later, the multigene panel results came back negative for any pathogenic mutations or variants in the *BRCA* genes but revealed a heterozygous pathogenic mutation in the *PMS2* gene c. 989-1G>T (IVS9-1G>T).

This pathogenic variant is denoted *PMS2* c.989-1G>T or IVS9-1G>T and consists of a G>T nucleotide substitution at the -1 position of intron 9 of the *PMS2* gene. The variant destroys a canonical splice acceptor site and causes abnormal gene splicing. Therefore, this mutation is classified as pathogenic and this in turn confirms the diagnosis of Lynch syndrome in the patient.

Risk reducing strategies: Following the NCCN guidelines for management of Lynch syndrome, the patient was offered colonoscopy every 1-2 years. Because the patient is a known case of bilateral fibrocystic mastopathy of the breast and due to her family history of breast cancer in addition to the identified *PMS2* mutation, the patient was advised to continue being on increased surveillance for breast cancer in the form of annual mammography and MRI. Because the patient had pursued TAH-BSO, her risk for endometrial and ovarian cancers is significantly reduced.

Discussion

In this case report, we presented two cases with classical HBOC phenotype due to personal and/or family history who were later found to carry pathogenic mutations in the *MMR* genes instead of *BRCA* genes through multigene panel. The first is a case of high grade serous ovarian cancer who presented to the genetics clinic with family history of young onset breast cancer and reported French Canadian ethnicity exhibiting a classical phenotype for HBOC. According to the international testing guidelines such as NCCN, this patient fits the criteria for HBOC due to her diagnosis of high grade serous ovarian cancer and her family history and is therefore eligible for *BRCA* testing. In addition, given the patient's French-Canadian ethnicity, this patient is at increased risk for *BRCA* mutations due to the known founder mutations in the French-Canadian population [11,12]. On the other hand, when assessing this patient's risk for Lynch syndrome using well known diagnostic criteria's such as Bethesda and Amsterdam guidelines, this patient is not eligible for Lynch syndrome testing. Although the patient was considered high risk for *BRCA* mutations, she was instead found to carry a pathogenic mutation in the *MSH2* gene confirming the diagnosis of Lynch syndrome.

Although the patient's mother was not available for testing, it is possible that her mother could have been also a carrier for the *MSH2* mutation due to the reported increased risk for breast cancer in *MSH2* carriers and especially in those of Canadian ethnicity as reported in Goldberg's study who reported cumulative life time risk for breast cancer in *MSH2* carrier reaching approximately 22% which is double the quoted 11% life time risk in the general Canadian female population [9].

In this case, we also show that immunohistochemical staining on the patient's ovarian cancer tissue had not identified any loss of nuclear expression of the *MMR* proteins although the patient carries a pathogenic mutation in the *MSH2* gene. This dis-concordance between IHC and germline results might be associated to several reasons: Most studies have evaluated *MMR* deficiency in colorectal and endometrial cancers but fewer studies have identified *MMR* deficiency in ovarian cancer, therefore, the clinical validity and utility of this test on ovarian cancer remains uncertain [11]. In addition, loss of nuclear expression is more commonly reported in ovarian epithelial tumors with non-serous histology including endometrioid, mucinous and clear cell subtypes than in other subtypes of ovarian cancers [11].

In the other case we presented in this case report, the patient was unaffected but presented to our clinic with family history of breast and

gastric cancer and a reported Ashkenazi Jewish ancestry from her maternal side. Looking at the patient's family history and her ancestry, this patient was considered at high risk for carrying mutations within the *BRCA* genes given the reported high prevalence of *BRCA* mutations in the Ashkenazi Jewish population which is estimated to be 1 in 40 due to the known founder effect [1]. However, multigene panel testing showed that this patient is negative for *BRCA* mutations but instead carries a mutation in the *PMS2* gene. Again, when assessing this patient's risk using international guidelines such as NCCN, Bethesda and Amsterdam criteria's, this patient is at significantly high risk for *BRCA* mutations but not for Lynch syndrome. This case supports the previous literatures which showed that Lynch syndrome families specifically those carrying *MSH6* and *PMS2* mutations may present with HBOC like phenotype [10].

Our cases suggest that in the absence of large panel testing, many of the *BRCA* negative HBOC like families might not be identified because they don't fit the known criteria for Lynch syndrome and therefore won't be eligible for *MMR* testing. As a result, those families might miss the opportunity from being identified and from being offered risk reducing strategies and targeted therapies such as immunotherapy which was recently FDA approved for patients with Lynch syndrome or *MMR* deficient solid tumors [13]. In addition, Phase I and Phase II studies have shown the benefit of using immunotherapy in locally advanced and metastatic breast cancers [14,15].

Our cases also suggest that the current Lynch syndrome diagnostic criteria's may not be sufficiently sensitive in identifying *MMR* mutations in HBOC like families. We therefore support the previous literatures which suggested the re-consideration of testing criteria's and that *MMR* testing should be considered in families with breast and ovarian cancers and those with HBOC phenotype [8].

Conclusion

From these case reports, we conclude that multigene panel testing has helped in providing a new perspective of Lynch syndrome and that Lynch syndrome should be considered in families with breast and ovarian cancers and especially in families with HBOC like phenotype. In addition, we suggest that *MMR* genes should be considered in the smaller panels such as breast cancer panels and that *BRCA* single gene testing might be spared to families with known familial mutations only.

In addition, we suggest that further studies should be undertaken to review the current Lynch syndrome testing criteria's in order to enhance their sensitivity in identifying individuals with Lynch syndrome who may present with HBOC like phenotype, so they can benefit from risk reducing strategies, targeted therapies and reproductive options.

Because there are no known established clinical guidelines for the management of breast cancer in individuals with Lynch syndrome, further studies should be undertaken to develop such guidelines and recommendations for women with Lynch syndrome.

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