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Case Reports and Review of the Literature

Lynch Syndrome and Breast Cancer: Case Reports and Literature Review

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ABSTRACT

In the era of advanced cancer genomics, our knowledge of hereditary cancer mutations continues to expand. Lynch syndrome is one of the hereditary cancer predisposition syndromes associated with an increased lifelong risk of several types of cancer development, such as colorectal, endometrial, ovarian and other. This unique syndrome is an autosomal dominant inherited disease caused by mutations on EPCAM gene or on mismatch repair genes, which lead to microsatellite instability. In this article we will present three such cases visiting our clinic. They had breast cancer and a familial or personal history of malignancy. This article summarizes what we consider important about Lynch syndrome and breast cancer.

Introduction

Lynch syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is one of the most common hereditary cancer predisposition syndromes and is associated with increased lifetime development risk of colorectal (CRC) and endometrial cancer (EC), as well as multiple other cancer types. The other types of cancer include ovarian, breast, stomach, small intestine, bile duct, pancreas, upper urinary tract, brain and skin carcinomas [1].

This syndrome is an autosomal dominant inherited disease. The oncogenic tendency of LS stems from a set of genomic alterations of mismatch repair (MMR) proteins. MMR genes are tumor suppressor genes that identify base-pair mismatches during DNA synthesis and repair them, allowing for accurate base pairing. Patients with LS are carriers of mutations in one of four DNA MMR genes: MLH1, MSH2, MSH6, PMS2 or the EPCAM gene upstream of MSH2 leading to its inactivation. More specifically MLH1, MSH2, MSH6 and PMS2 mutations in this syndrome account for approximately 37%, 41%, 13% and 9% respectively [2]. The total risk of breast cancer up to 70 years of age in MLH1 carriers is 18.6% and in MSH2 carriers 11.2% [3].

Considering these facts, it is important to diagnose LS as early as possible, because of the increased lifetime risk of developing cancer. The diagnosis of LS is based on clinical suspicion. If a patient with family history meets the Amsterdam II or Bethesda criteria, the patient is facing a high possibility of LS (Table 1). Unfortunately, this is not always the case, as only 50% of patients qualify for these criteria [2]. Because of that, it is necessary to perform genetic testing on people who are suspected LS carriers. Testing is usually performed with blood sample, but also saliva/buccal swab, skin biopsy or tumor tissue can be used [4].

It is fairly well known that LS is caused by an autosomal dominant mutation in DNA mismatch repair genes, leading to microsatellite instability (MSI). Screening for MSI or DNA mismatch repair problems are the initial step for diagnosis. Germline mutations of the MMR genes MLH1, MSH2, MSH6 and PMS2 are diagnostic for LS. We can use immunohistochemical analysis (IHC) for loss of expression in MMR proteins or use polymerase chain reaction-based test for MSI [2].

Most of patients with LS are presenting with different types of cancer. The age of these patients is usually under 50 years. Treatment of these people includes surgery and adjuvant therapy. In this study, we describe three different cases of LS with breast cancer. Breast cancer is not common in the frame of LS. The aim of this report is to understand LS and get acquainted with LS presenting breast cancer.

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Table 1: Amsterdam II criteria and revised Bethesda guidelines.

Amsterdam II criteria:
i.Three of more relatives with histologically verified Lynch syndrome-associated cancer, one of whom is a first-degree relative of the other two*
ii.Cancer involving at least two generations
iii.One or more cancer cases diagnosed before 50 years old of age
Revised Bethesda guidelines:
i.Diagnosis of colorectal cancer or endometrial cancer in a patient younger than 50 years age
ii.Presence of synchronous colorectal cancers, metachronous colorectal cancers, or other Lynch syndrome-associated tumors, regardless of patient age
iii.Diagnosis of colorectal cancer with a high frequency of microsatellite instability on the basis of histologic findings (Crohn's-like lymphocytic reaction, mucinous or signet-ring cell differentiation, or medullary growth pattern) in a patient younger than 60 years of age
iv.Diagnosis of colorectal cancer in one or more first-degree relatives with a Lynch syndrome-related tumor, with one of the diagnoses occurring before 50 years of age
v.Diagnosis of colorectal cancer in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of patient age

*Lynch syndrome-associated tumors include cancers of the colon and rectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel and sebaceous glands, as well as keratoacanthomas.

Case Presentations

We report 3 different cases of women presenting to our hospital with breast malignancy, later revealing LS. Our first patient was a 68-year-old Caucasian woman with a personal history of thyroid, endometrial and breast cancer. Her family history was not fully known since she was adopted. The woman was treated for a new ductal carcinoma *in situ*, in the contralateral breast. Taking her personal history into consideration, mastectomy and sentinel node examination was performed. Genetic testing with blood sampling was executed. Our patient was positive for mutation in MSH6 gene and the diagnosis of LS syndrome was imposed.

A pathogenic mutation is a variant in the DNA sequence of genes that affects their ability to function. The MSH6 gene is a tumor suppressor gene, so it slows down cell division, repairs DNA mistakes and defines cell death. When it does not work properly, cells can grow out of control and lead to cancer. Mutations in the MSH6 gene that are abnormal, are most likely inherited from either parent and can cause LS. These mutations are linked to increased cancer risk: colorectal, uterine, ovarian, breast in women; brain, colorectal, hepatobiliary tract, pancreatic, prostate, stomach and urinary tract in men. Having a mutation in the MSH6 gene does not necessarily mean the development of cancer but expresses an increased risk [5].

Our second patient was a 60-year-old Caucasian woman with a personal history of endometrial cancer. She had a family history of her sister developing ovarian cancer. She presented to our hospital with microcalcifications in mammography and breast cancer diagnosis was finally made. After the genetic testing being performed because of her personal and family history (type of sample: saliva), LS was revealed (MSH6 gene, mutation 9). Mutations in MSH6 gene and their relevance have already been discussed.

Our third patient was a 45-year-old Caucasian woman with no previous personal history of cancer. Her sister developed breast cancer at the age of 36, with no other family history recorded. She presented to our hospital with a new finding in her initial screening mammography. Diagnosis of breast cancer followed. Genetic testing (saliva sampling) was offered because of her family history. Our patient was positive for mutation in PMS2 gene and the diagnosis of LS syndrome was made.

The PMS2 gene is also a tumor suppressor gene. Mutations in the PMS2 gene that are abnormal are most likely inherited from either parent and can cause LS. These mutations are linked to increased cancer risk: colorectal, uterine, ovarian, breast in women; colorectal, prostate, renal and small intestine cancers in men. Research on this gene is ongoing, so the estimated risk of cancer is variable [6]. We observed that none of these women met the Amsterdam or Bethesda criteria for diagnosis of LS and two out of three had the same mutation (MSH6 gene) (Table 1).

Discussion and Conclusion

Breast cancer is the most common cancer to diagnose (excluding skin cancer) and is the second leading cause of cancer death among women, after lung cancer [4]. Moreover, endometrial cancer is the fifth most common cancer in women living in developed countries. Approximately 5% of all endometrial cancers and 1% of ovarian cancers are occurring because of LS mutation [2]. The lifetime cancer risk for these women is 5-14% for breast cancer, 4-12% for ovarian cancer, 30-70% for colon cancer and 30-60% for endometrial cancer respectively [7]. It is important to distinguish with genetic screening testing if cancer in each case is sporadic or hereditary. This appears most important for high-risk women diagnosed with either endometrial or colorectal cancer. Every woman who presents with a family history of breast or ovarian cancer should be offered genetic consultation and the chance of genetic testing, according to the recommendations of the Society of Gynecologic Oncology (Table 2).

Breast cancer associated with known LS constitutes a challenge for the medical community [8]. Interestingly enough, there is an increased risk of breast cancer for this specific population [9]. Research regarding MMR genes indicates that MSH6 mutation related to breast cancer associated with LS, may present more often than other mutations [8]. Women with LS are also at increased risk for several malignancies. Risk management guidelines for LS carriers exist in order to decrease cancer-related mortality [1]. For these patients, annual colonoscopy initiating at the age of 20 to 25 or 2-5 years earlier than the youngest patient in the family is recommended. This should be repeated every 1 to 2 years. Colectomy can be performed if colon cancer is diagnosed or if an adenoma that cannot be otherwise excised is revealed [7].

Table 2: SGO guidelines for genetic risk assessment for Lynch syndrome.

Risk Assessment Helpful	Risk Assessment recommended
Patients with endometrial or colorectal cancer diagnosed before 50 years. Patient with endometrial or ovarian cancer with synchronous or metachronous Lynch-associated malignancies. Patients with colorectal or endometrial cancer and more than 2 first/second-degree relative meeting the above criteria.	Patient meeting revised Amsterdam criteria.* Patient with synchronous oi metachronous colorectal and ovarian or endometrial cancers. Patient with a first/second-degree relative with a known MMR mutation.
Patient with one of the above criteria have a 5-10% chance of Lynch Syndrome.	Patient with one of the above criteria have a 20-25% chance of Lynch Syndrome.

*Revised Amsterdam criteria are as follow: 1) at least 3 relatives with LS-associated cancer in 1 lineage 2) one affected individual is a first-degree relative of the other two 3) at least two successive affected generations 4) at least 1LS-associated cancer is diagnosed before age 50 years.

Additionally, gynaecologic screening includes annual pelvic examination, transvaginal ultrasound, CA-125 evaluation and routine endometrial aspiration beginning at age 30-35, or 3-5 years before the earliest age of diagnosis of gynaecologic cancer in the family. Nevertheless, the efficacy of this plan remains uncertain. Risk-reducing surgery with hysterectomy and bilateral salpingo-oophorectomy can reduce both the incidence and mortality in women with LS. It is suggested in women older than 35 years having completed childbearing [2]. Chemoprophylaxis (aspirin or progestin) appears to be of some help in LS but has not been studied thoroughly. Breast cancer screening is currently based on the estimated individual risk deriving from personal and family history. Specific screening recommendations are not available [7]. In some situations, prophylactic surgery appears to be helpful or necessary.

In conclusion, it is important to recognize individuals who may have Lynch Syndrome and belong to a high-risk group. Extensive genetic testing provides valuable data, especially if a personal history of breast cancer exists, giving the chance to implement testing to this sub-group of patients according to newer recommendations [10]. People with this syndrome should be advised on the benefits of prophylactic surgery for ovarian, endometrial, breast and colon cancer. However, this decision is difficult and a multidisciplinary medical team must be prepared for supporting these women physically and psychologically. Above all, patients should be advised to communicate with family members regarding accumulated cancer risk and their indication for testing, screening, and surveillance. Family members at risk should be offered genetic counseling and testing.

Highlights

i. It is important to recognize individuals who may have Lynch Syndrome through widened genetic testing.
ii. There is an increased risk of breast cancer in patients with Lynch-associated cancers.
iii. Specific management of Lynch carriers should be followed, including screening and intervention.

Author Contributions

Spyridon Marinopoulos: Author; Eleni Papamattheou: Formatted and submitted the manuscript; Sofia-Dionysia Touriki: Reviewed the literature; Aris Giannos: Surgeon, Breast Unit; Constantine Dimitrakakis: Head of Breast Unit.

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