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Case Report

Carcinomas Associated With Lynch Syndrome: A Family History

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Lynch syndrome is a rare and inherited defect disorder. People who have Lynch syndrome are strongly predisposed to develop colorectal cancer as well as several other types of cancer. The aim of this study was to explore features of ovarian cancers arising in families with Lynch syndrome. This study was a case report based on family history examining three patients with a new diagnosis of colorectal adenocarcinoma with ovarian cancer. Family members of carriers of the mutations were counseled, and those found to be at risk were offered mutation testing. The clinical criteria of the Amsterdam II guidelines for Lynch syndrome were used in this study. This is a maternal history of a 27-year-old woman sharing the destiny of her 48-year-old mother and 45-year-old aunt, both of which were suffering from Lynch syndrome associated with ovarian cancer. The maternal grandmother and maternal uncle of this young woman also suffered from colon cancer in their forties. The medical implications for the carrier relatives were considered as the maternal branch of the family.

Key words: Lynch syndrome – Hereditary nonpolyposis colorectal cancer – Ovarian cancer

Lynch syndrome is an autosomal dominant cancer-susceptibility disorder caused by mutations in the DNA mismatch repair genes (MMR), usually the MLH1 or MSH2 genes or less frequently the MSH6 or PMS2 genes.[1] Mutations in any of these genes prevent the proper repair of DNA replication mistakes. As the abnormal cells continue to divide, the accumulated mistakes can lead to uncontrolled cell growth and possibly cancer.[1,2] In the early 1900s, Dr. Alfred Warthin identified a family with multiple family members affected with colorectal and endometrial cancer in several generations.[2] In the 1960s, Dr. Henry Lynch and colleagues identified families with striking increases in the incidence of colorectal, gastric, endometrial, and ovarian cancers. Dr. Lynch's group termed this the cancer family syndrome; it has subsequently become known as the Lynch syndrome and hereditary nonpolyposis colorectal cancer (HNPCC).[3]

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The syndrome is not common, having a prevelance of one or two of every 1000 people. This syndrome is responsible for 3% to 5% of all diagnosed cases of colorectal cancer.[4,5] The syndrome is classified as type I in the absence of extracolonic cancers and type II, if these are present, particularly carcinomas of the endometrium and the ovary.[3] It tends to occur at a younger age than in most other colorectal cancer cases.[5,6] Several sets of clinical criteria have been developed to help identify families that are likely to have Lynch syndrome; the two most commonly used sets of criteria are the Amsterdam II criteria and the revised Bethesda guidelines. The Amsterdam criteria are fairly specific for Lynch syndrome, but are not very sensitive.[2,5,7-9] Individuals with HNPCC have about an 80% lifetime risk for colon cancer.[7] Affected individuals with HNPCC also have an increased risk of having endometrial, ovarian, stomach, small intestinal, hepatobiliary, upper urinary tract, brain, and skin malignancies.[6] Endometrial and ovarian cancer is the most common extracolonic tumor in this syndrome. In HNPCC, women with a MMR gene mutation, have a 40% to 60% cumulative lifetime risk for endometrial cancer and 8% to 12% for ovarian cancer.[9,10] Therefore female members of HNPCC families are offered a gynecologic examination, a transvaginal ultrasound, and serum level CA-125 analysis to be performed annually, starting at 25 years of age. The theoretical benefit of such programs is early detection of (pre)malignant lesions, thereby reducing morbidity and mortality due to endometrial (and ovarian) cancer. In addition, risk-reducing surgery consisting of prophylactic hysterectomy and bilateral salpingo-oophorectomy should be offered to women aged 35 years or older who do not wish to preserve their fertility.[11,12]

There are no premonitory physical signs or biomarkers of genotypic risk in the family history of individuals who have Lynch syndrome that can provide important clues as to its presence. Lynch syndrome is under-recognized, even when patients have clear criteria unrelated to family history.[10] Therefore, considering the nature of the Lynch syndrome, the assessment of the family history is of crucial importance for survival of patients, which decreases mortality and morbidity.[11] Health care professionals play a critical role in assessing colorectal cancer risk and providing care for patients with Lynch syndrome, including identifying patients who would benefit from genetic counseling, providing education, and assessing and meeting patient psychosocial needs.[8,9]

The aim of this study is to describe the experiences of three members of the same family who had colonic and ovarian cancers.

Case Report

In February 2008, a 27-year-old woman complaining of epigastric discomfort—which she described as headaches, burning in her throat, fatigue, palpitation, dyspnea, abdominal pain and bloating, and constipation—was admitted to the Gynecologic Oncology Unit of our hospital. She had just married, was gravida 0, para 0, and a nonsmoker and nondrinker. She had a medical history of thyroid nodules. The remainder of the examination was normal. A more detailed history by the patient revealed that multiple cancers had occurred in her family (her maternal grandmother and maternal uncle both died of colorectal cancer). Because of her family history, the patient underwent abdominal computed tomography (CT) and it revealed a bilateral ovarian mass (6 cm), and metastatic implants at the omentum, sigmoid, and rectum, and a 9-mm hypodensity in the left lobe of the liver. The morphology and location of our patient's colorectal lesion are of interest and highlight the typical features of HNPCC. CA-125 assay was 2876 U/mL. The patient elected to have surgery, and the exploratory laparotomy included total abdominal hysterectomy, salpingo-oophorectomy, appendectomy, pelvic and periaortic lymph node dissection, and omentectomy. The pathology report revealed invasive, moderately differentiated serous adenocarcinoma. (The pattern is that of high grade morphologic dysplasia consistent with invasive intraepithlelial.) She was staged at IIIC grade 2. The patient recovered quickly from the surgery. Chemotherapy was planned after surgery with 6 courses of intravenous paclitaxel and carboplatin once every 3 weeks. The patient was completely asymptomatic during and after the 6 cycles of chemotherapy. Clinical evaluation and diagnostic tests were all within the normal ranges after the chemotherapy ended and a second-look laparotomy was planned according to our clinic's policy. The patient was monitored for 1 year, and there were no abnormalities. CA-125 values and clinical examinations were all within the normal range during this time period. One year later, she came to the outpatient gynecology clinic of our hospital with the complaint of abdominal pain. Her CA-125 level was increasing again. A CT scan showed a new peritoneal implant on the liver and an increase in

size of the pelvic mass adjacent to the rectum. She underwent debulking, proctocolectomy with colostomy and intraperitoneal (IP) port placement, and subsequently received 4 cycles of IP cisplatin. She was healthy for another 6 months until her CA-125 level began to increase again. Then, she was treated with 3 cycles of liposomal doxorubicin. Unfortunately, she experienced palmar plantar erythema with desquamation of her trunk. As a result she had to discontinue the therapy. Instead, she received 9 courses of topotecan for 5 days every 3 weeks. After her last session of chemotherapy, she felt better.

As a reflection of her hard times on her private life, she got divorced from her husband while on treatment and she decided to stay with her family. She was angry that her husband could not share this big task. She was also angry with herself for not taking necessary care and getting checked when the symptoms of constipation, abdominal pain, and bloating first started a couple of years ago. She stated strong discontentment of having to save her life at the cost of her fertility. As a result she regularly received psychologic support from her family and psychiatrist. At present, she feels much relieved but still has concerns about the future.

When the patient was first diagnosed, a family history of this syndrome was only known in the maternal grandmother and maternal uncle. Being aware of the extended family history is the first step in the recognition of individuals ''suspect'' for hereditary colon cancers such as Lynch syndrome. She was informed about hereditary colon cancer to make her understand that she was at risk. The brochure recommended genetic consultation for any person who had two or more relatives with colon cancer. Finally, she underwent genetic testing and was informed that she had the MLH1 gene mutation for HNPCC. Tumors observed in Lynch syndrome are diagnosed at an unusually early age.

Concurrently the patient's maternal aunt (gravida 2, para 2) has seen us for abdominal bloating and abnormal bleeding between menstrual periods. She is a married housewife with a daughter who has polycystic ovary syndrome. She had been diagnosed with colorectal cancer arising in the cecum and with cancer of the ovary at age 45 years. Further analysis revealed an elevated CA-125 tumor marker. We were aware that ovarian cancer is one of the diseases that show up frequently among families with HNPCC. The patient's aunt had also undergone HNPCC genetic testing and was found to have a mutation in the MLH1 gene. We carried out total abdominal hysterectomy, salpingo-oophorectomy, appendectomy, pelvic and periaortic lymph node dissection, omentectomy, and hysterectomy. The pathology report revealed invasive, poorly differentiated serous adenocarcinoma. Multiple courses of chemotherapy were provided. CA-125 level decreased from 253 to 55 units (U/ml). After a 9-month disease-free interval, the patient had gained about 5 lbs and was back to her precancer weight. She has been undergoing regular screenings for the disease as part of her health care routine. She seems strong and is coping with the situation.

The importance of enhanced surveillance for early diagnosis and prevention of disease is a critical part of primary care. It is imperative that health care providers obtain a minimum of a three-generation pedigree, recognize hereditary cancer patterns, and provide referral counseling for genetic testing of individuals suspect for Lynch syndrome. Therefore, we wanted to see the patient's mother. The mother (gravida 1, para 1) had menometrorrhagia, back pain, vaginal discharge, and hypothyroid disease. We diagnosed an ovarian tumor with colorectal cancer at age 48 years. She underwent total abdominal hysterectomy, salpingo-oophorectomy, appendectomy, pelvic and periaortic lymph node dissection, omentectomy, and hysterectomy. The pathology revealed invasive, moderately differentiated serous adenocarcinoma (arising in ovary serous adenocarcinoma scattered diffusely with direct invasion into the peritoneum and rectosigmoid colon). Chemotherapy was planned after surgery with 6 courses of intravenous paclitaxel and carboplatin once every 3 weeks. She tolerated it well, but she began to develop nausea and numbness in the toes bilaterally with no serious decrease in blood cell counts. CA-125 level was stable for about 6 months. After 4 weeks, her CA-125 level began to decrease. The patient was feeling well with no nausea, no diarrhea, and just minimal pains. A repeat CT scan reported a ''slight increase'' in abdominal metastases. She experienced disease recurrence and started her second round of treatment, which lasted another 6 months. Tolerating the treatment well, she is now back at home. She has checkups at the hospital every 3 months for surveillance examinations and routine CA-125 checks.

Discussion

We present a patient with a family history of multiple cancers. This report illustrates several warning signs that should alert a provider that a

patient may have Lynch syndrome and highlights some of the critical issues clinicians face when diagnosing and managing these patients.

HNPCC is associated with a 52% lifetime risk of developing colorectal cancer in women and a 69% risk in men. Genetic mutations for ovarian cancer have become a hot topic of research. Currently, there are 3 genetic syndromes (ovarian cancers associated with colon and endometrial cancers, breast and ovarian cancer syndrome, and site-specific ovarian cancer syndrome) that are recognized to increase ovarian cancer risk. The risk of developing ovarian cancer in patients with Lynch syndrome is about 12%, roughly 10 times the baseline population risk.[3,9] The other female members of the family have a lifetime risk of about 50% of developing ovarian cancer. Familial ovarian cancers tend to occur at an early age, before 50 years, and tend to be advanced serous epithelial cancers.[4] Other than age, the next most important risk factor is a family history of ovarian cancer, particularly if family members are affected at an early age. If your mother, sister, or daughters have had ovarian cancer, then you have an increased risk of developing the disease.[8] In a different study,[6] 130 families, all of whom had at least one member suffering from Lynch syndrome, were examined. Among those with Lynch syndrome 7 had small intestinal cancer, 13 had cancer of the ureter, 2 had kidney cancer, 19 had ovarian cancer, and 22 had pancreatic cancer. Of these cancers, 70% were diagnosed before the age of 50 years. Another study[7] revealed that the average age for diagnosis of ovarian cancer in women with Lynch syndrome is 44 years. Several recent population-based studies suggest that the cumulative colorectal cancer risk may be as low as 30% to 45% and that the median age of diagnosis of colorectal cancer in individuals with Lynch syndrome may be as high as 60 years when adjusted for referral bias.[9–11] In our case report, the patients were diagnosed at age 27, 45, and 48 years.

There are no obvious symptoms of ovarian cancer in the early stages of the development of this disease. Occasionally an ovarian cyst will be detected on a routine gynecologic examination. A cyst can break and bleed and that will cause enough symptoms for the woman to seek help. Otherwise, most ovarian cancers are found when it is somewhat advanced, because early stage ovarian cancers rarely cause symptoms.[5] Studies indicate that some women with cancer of the ovaries may experience persistent, nonspecific symptoms, such as bloating, pelvic or abdominal pain, difficulty in eating, or a state of feeling full quickly, and/or urinary urgency or frequency.[4,12] Our patients mentioned symptoms such as abdominal bloating, constipation, and abnormal bleeding between menstrual periods. When the family history of 130 individuals with documented HNPCC was examined the genetic distribution was found to be MSH2 (n = 64), MLH1 (n = 62), and MSH6 (n = 4).[6] Our 3 patients underwent HNPCC genetic testing and were found to have a mutation in the MLH1 gene. It should also be noted that only 3 of all of the family members counseled accepted to receive the genetic testing.

Lu *et al*[11] included 104 studies with pretest genetic counseling. There was good efficacy in improving knowledge about HNPCC and decreasing depression and distress levels among family members of HNPCC with cancer. About 1 million individuals in Western Europe are at risk for Lynch syndrome.[1] Vasen *et al*[13] performed a survey to evaluate the strategies currently used to identify individuals at high risk for colorectal cancers (CRC) in 14 Western European countries. The cost-effectiveness of this approach should be further evaluated. All countries with a colorectal cancer population screening program should obtain a full family history as part of patient assessment. In addition, counseling is an important component of the management of any family with Lynch syndrome.[1,11–13]

In summary, we described a family with an unusual presentation of Lynch syndrome. The importance of enhanced surveillance for early diagnosis and prevention of disease is a critical part of primary care. Thus, it is imperative that health care providers, especially nurses, should develop an awareness of hereditary cancer patterns, and provide referral counseling for genetic testing of individuals suspect for Lynch syndrome.

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