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Diagnostic challenges in the diagnosis and treatment of ovarian cancer in Lynch syndrome

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Abstract

Introduction and purpose

Lynch syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant genetic disorder characterized by a significantly increased risk of developing various malignancies, including ovarian cancer. This study aims to analyse the risk of ovarian cancer development in patients with Lynch syndrome and to compare the diagnostic and therapeutic approaches for this neoplasm in the context of sporadic cases.

Description

This discussion explores the genetic mechanisms underlying mutations in mismatch repair (MMR) genes, such as MLH1, MSH2, MSH6, and PMS2, which are essential for maintaining genomic stability. The diagnostic criteria, including the Amsterdam Criteria and the Bethesda Guidelines, are reviewed. The paper highlights the diagnostic challenges posed by the nonspecific symptoms of ovarian cancer and emphasizes the importance of early detection and monitoring.

A comprehensive review of treatment modalities is also provided, covering surgical cytoreduction, chemotherapy, and emerging therapies, such as immunotherapy and cancer vaccines. The importance of interdisciplinary care for patients is underscored, along with the need for preventive measures and health education to manage cancer risk.

Summary

Despite the challenges associated with diagnosis and treatment, the prognosis for patients with ovarian cancer linked to Lynch syndrome is generally more favourable than for those with sporadic cancers. This can be attributed to earlier diagnosis and the favourable histopathological characteristics of tumours associated with Lynch syndrome.

Keywords:

Lynch syndrome; ovarian cancer, mismatch repair, microsatellite instability; cancer vaccines.

Introduction and purpose

Lynch syndrome (LS), or hereditary non-polyposis colorectal cancer, is a familial genetic syndrome inherited in an autosomal dominant fashion. The syndrome is mainly associated with

a predisposition to colorectal cancer; however, there is also an increased predisposition to cancers of the endometrium, ovaries, stomach, urinary tract (including kidney, renal pelvis, ureter, bladder and prostate), pancreas, biliary tract, small bowel, and brain [1]. For this reason, Lynch Syndrome I is characterized by cancer occurring solely in the colon, while Lynch Syndrome II includes cases where other cancers coexist alongside colon cancer [2].

LS is caused by mutations in mismatch repair (MMR) genes, such as MLH1, MSH2, MSH6, and PMS2, and rarely in the EPCAM gene, which can silence the MSH2 gene epigenetically [3]. Each mutation carries a different risk of ovarian cancer [tab 1].

Table 1. Ovarian cancer incidence statistics by specific mutation (NCCN Clinical Practice Guidelines in Oncology) [4]

Mutation	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 years	Cumulative Risk for Diagnosis Through Lifetime for General Population
MLH1	46 years	4%–20%	1.1%
MSH2	43 years	8%–38%	1.1%
MSH6	46 years	≤1%–13%	1.1%
PMS2	51–59 years	1.3–3%	1.1%

Studies suggest that the penetrance of particular genes depends on the sex of the carrier and various environmental factors. These factors include body weight, alcohol consumption, gut microbiota composition, diabetes, and the intake of medications such as acetylsalicylic acid (aspirin) or ibuprofen [5]. It is important to note that a definitive diagnosis of LS requires genetic testing [6].

Lynch syndrome-associated ovarian cancer (LS-OC) is the second most common extra intestinal sentinel cancer of LS, with an estimated probability of 17% for developing OC [7]. This article reviews the research progress on LS-OC, covering genetic changes, clinicopathological characteristics, screening, diagnosis, surveillance, prevention, and treatment.

Material and methods

The review was based on the analysis of materials collected in the „PubMed" and Google Scholar. The following keywords were entered during the search for scholarly articles: Lynch syndrome; ovarian cancer, mismatch repair, microsatellite instability; cancer vaccines. A total of 34 articles published between 2016 and 2024 were considered for the study and verified for their relevance to the topic of Lynch syndrome-related ovarian cancer.

Diagnosis

For the initial assessment of Lynch syndrome, clinicians utilize the Amsterdam II criteria and the revised Bethesda guidelines. The Amsterdam II criteria require at least three relatives to be diagnosed with cancers associated with Lynch syndrome, and the fulfilment of additional conditions: the cancers must occur in at least two generations; one patient must be a first-degree relative of the other two; at least one diagnosis must occur before the age of 50; there should be no evidence of familial adenomatous polyposis; and the diagnoses must be confirmed through pathomorphological examination [tab 2].

In contrast to the Amsterdam Criteria, the Revised Bethesda Guidelines use pathological data in addition to clinical information to help health care providers identify persons at high risk [7]. The revised Bethesda guidelines include the following criteria for testing: Colorectal cancer diagnosed in a patient under the age of 50; Presence of synchronous or metachronous colorectal or other Lynch syndrome-related tumours, regardless of age; Colorectal cancer exhibiting microsatellite instability; Colorectal cancer diagnosed in a patient with at least one first-degree relative who had Lynch syndrome-related cancer, provided one of the cancers was diagnosed before age 50; Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with Lynch syndrome-related cancers, regardless of their ages.

If a person meets any one of these five criteria, their tumour(s) should be tested for microsatellite instability [6][tab3].

Table 2. Amsterdam criteria II (Bui QM, Lin D, Ho W. 2016) [8]

Three or more family members with HNPCC-related cancers, one of whom is a first-degree relative of the other two
Two successive affected generations
One or more of the HNPCC-related cancers diagnosed under age 50 years
Familial adenomatous polyposis (FAP) has been excluded

Table 3. Revised Bethesda Guidelines (Vindigni SM, Kaz AM. 2016) [9]

Colorectal cancer diagnosed before age 50
Presence of synchronous or metachronous colorectal or other Lynch syndrome associated cancers (e.g. cancers of endometrium, ovary, stomach, small bowel, pancreas, biliary tract, ureter, renal pelvis, brain, sebaceous glands, keratoacanthomas)
Colorectal cancer with MSI-high pathology in a person who is younger than 60 years of age
Colorectal cancer diagnosed in a person with one or more first-degree relative with colorectal cancer or Lynch syndrome associated tumour diagnosed under age 50
Person with colorectal cancer and two or more first- or second-degree relatives with colorectal cancer or Lynch syndrome associated cancer diagnosed at any age.

Ovarian cancer symptoms

OC is the leading cause of death from gynaecological cancers in developed countries. Due to its vague or nonspecific symptoms, diagnosis can be challenging. As a result, many patients often present to their doctors at an advanced stage of the disease [10].

Symptoms of OC include abdominal pain bloating as well as irregular menstrual periods, dizziness or balance issues, and balance issues. Non-specific gastrointestinal symptoms, such as nausea or changes in bowel habits, may appear and persist for a few weeks, often worsening as the disease progresses. Advanced stages of OC may lead to ascites, the accumulation of fluid in the abdominal cavity, which can cause abdominal distension and respiratory difficulties. Vaginal bleeding is a rare symptom of OC but may occur in some cases [11].

Diagnosis

It should come as no surprise that in women with LS, OC is revealed more often and earlier than in people without genetic mutations. The average age of onset is 46, while in women without this syndrome it is usually after the age of 60 [12,13,14]. Due to the above fact, doctors should never ignore any symptoms, even in women of a relatively young age. Early

diagnosis is the key to effective treatment and survival of patients. Unfortunately, these symptoms are non-specific and appear relatively late [15,16].

Diagnosis of LS-OC in patients does not differ significantly from that of this type of sporadic tumour. However, additional diagnostic factors, such as family history, genetic testing, microsatellite instability testing, and patient monitoring, should not be overlooked. From a clinical perspective, diagnosing OC remains a significant challenge, as it is often detected at an advanced stage [17].

The gold standard for diagnosis remains histopathological examination of tumour tissue. The most common histopathological type is mixed cancer (endometrial/clear cell/mucinous), followed by endometrial cancer. The third and fourth most common types are serous and clear cell cancers, respectively. Rare cases of borderline and mucinous tumours are also observed [14,18].

Every surgical procedure involves some degree of risk, which is why ongoing research focuses on identifying biomarkers to differentiate between benign and malignant lesions. Currently, transvaginal ultrasound (TVUS), MRI, and markers such as CA125 and HE4 are commonly used in diagnostics.

CA125 is an antigenic glycoprotein. Elevated levels of CA125 may indicate OC; however, despite being the most commonly used marker for this malignancy, its specificity is low. CA125 levels can also increase in conditions such as endometriosis, adenomyosis, inflammatory states, pregnancy, and in cancers of the breast, uterus, stomach, pancreas, liver, and colon. Its sensitivity in detecting early-stage OC is also limited, ranging from approximately 50% to 60%. Additionally, this marker is used to monitor treatment efficacy and detect disease recurrence. To enhance sensitivity, several measurement techniques for the glycoprotein CA125 have been developed. These include immunoenzymatic assays utilizing anti-MUC16 (OC 125) and IgM (M11) antibodies, a novel ELISA antibody-lectin test, detection of CA125 in exosomes, and identification of CA125 glycoforms. While these strategies represent improvements, they remain imperfect and require further investigation.

HE4 is a protein subtraction derived from epithelial cells of the epididymis and is overexpressed in ovarian cancer tissues. Unlike CA125, HE4 levels are less influenced by conditions such as endometriosis or benign ovarian tumours. However, its concentration can also increase in other malignancies, including lung, pancreatic, and breast cancers, as well as in patients with kidney failure. Since single markers remain insufficient, the RMI index and the ROMA test are commonly employed. The RMI index is calculated as the product of ultrasound findings, menopausal status, and CA125 concentration (U/ml). In contrast, the

ROMA test integrates CA125, HE4, and menopausal status to estimate malignancy risk [19,20].

Innovative and promising diagnostic approaches include miRNA-204, hepcidin, MAGP2, and the analysis of gene methylation levels in cfDNA. However, further research is needed to validate and improve their diagnostic utility in OC [16,21].

Features observed during transvaginal ultrasound that suggest malignancy include a tumour diameter exceeding 100 mm, multilocular structure, thick septations, excrescences within the lumen, solid components, bilateral tumours, and the presence of free fluid in the abdominal cavity. Artificial intelligence shows promise in differentiating masses on ultrasound with greater sensitivity than radiologists. However, further time and extensive studies are required to evaluate its effectiveness and, most importantly, its impact on patient survival [22,23,24].

Next-generation sequencing (NGS) represents the next diagnostic step for individuals with clinical indications of LS who have negative microsatellite instability (MSI) and immunohistochemical (ISH) test results. It can also serve as a definitive confirmation method for individuals with positive results from these tests. The sensitivity of NGS for detecting Lynch syndrome ranges from 96% to 100%, while its specificity varies between 97% and 100%.[7,25] NGS is the gold standard; however, it is an expensive test, which is why IHC diagnostics and MSI analysis are recommended first. IHC and MSI can be used separately, but performing them together increases sensitivity and specificity. If the result of either test is positive, it should be confirmed with NGS testing [15].

The microsatellite instability (MSI) test relies on PCR analysis to compare changes in short repetitive sequences across multiple loci. An instability rate of 30% is considered a threshold for determining the presence of MSI. The sensitivity of this test for detecting Lynch syndrome ranges from 55% to 91%.

Immunohistochemical tests are designed to detect the absence of protein expression encoded by mismatch repair (MMR) genes. The primary targets are the MLH1 and MSH2 genes, as abnormalities in these genes account for approximately 70% of identified Lynch syndrome cases. Some centers also test for the MSH6 and PMS2 genes either as part of initial diagnostics or when no abnormalities are found in MLH1 and MSH2. Depending on the diagnostic approach, two-color or four-color staining methods are employed [7, 25].

Treatment and prognosis

Surgical cytoreduction is crucial for patients with both sporadic ovarian cancer and those with Lynch syndrome. Adjuvant chemotherapy typically involves platinum derivatives (carboplatin,

cisplatin) and paclitaxel [26]. Studies on the effect of adjuvant therapy in patients with ovarian cancer and MMR deficiency have yielded conflicting results, and no recommendations can be made regarding initial chemotherapy. However, studies on the use of immunotherapy are promising. Pembrolizumab, a monoclonal antibody that inhibits T cell apoptosis by blocking the PD-1 receptor, is approved for the treatment of all cancers except colon cancer. Studies have shown that in patients with MMR deficiency and gynecological cancers, pembrolizumab achieves an objective response rate of 34.3%, making it a potential treatment option [7,27]. The most ground-breaking research appears to focus on cancer vaccines. These could be used not only for prevention but also to reduce the risk of progression. Their purpose is to stimulate the body to recognize and combat cancer cells [28,29,30].

The good news is that survival rates for ovarian cancers associated with Lynch syndrome are higher than those for sporadic cancers. This is due not only to rapid diagnosis but also to the histopathological features of these tumours. In most cases, they are well or moderately differentiated and are diagnosed at FIGO stages I or II [7,15,31].

The 5-year survival rate exceeds 80 percent, regardless of which gene is mutated [32].

Screening and prevention

There is insufficient evidence to suggest that periodic gynaecological examinations improve survival in women with LS. A large randomized controlled trial indicates that transvaginal ultrasound and Ca125 testing in the general population do not reduce mortality [15,33]. Women with LS should begin regular gynaecological examinations at the age of 25. These visits aim not only to monitor health status but also to educate patients about potential cancer symptoms. Regarding endometrial cancer prevention, transvaginal ultrasound (TVUS) lacks sufficient sensitivity and specificity, which is why it is not routinely recommended. However, a physician may consider this examination in appropriate circumstances. In collaboration with the patient, the gynaecologist may also consider performing an endometrial biopsy every 1–2 years, starting at ages 30 to 35. Care management for patients with LS should be interdisciplinary. In addition to the above recommendations, patients should undergo annual colonoscopy beginning at ages 20 to 25, and gastroscopy every three years starting at age 40 [4]. Prophylactic hysterectomy and bilateral salpingo-oophorectomy(BSO) effectively reduce the risk of gynecologic cancers in women with Lynch syndrome. However, these are major surgical procedures that carry significant risks and potential side effects, which may adversely

impact the patient's quality of life. Whenever possible, these surgeries should be performed laparoscopically to facilitate faster recovery.

The decision to proceed with hysterectomy and BSO should be made on an individual basis, considering the patient's age, cancer risk, and reproductive plans. This personalized approach helps determine the optimal timing for the procedure. For women with mutations in the MSH2 or MLH1 genes, surgery is typically recommended around age 35, while for those with MSH6 mutations, it may be considered a few years later, around age 40. Following surgical menopause, patients should receive hormone replacement therapy until they reach the age at which they would naturally experience menopause. Estrogen therapy can alleviate symptoms such as vaginal dryness, urinary incontinence, decreased libido, and cognitive decline, while also reducing the risk of osteoporosis and cardiovascular diseases.

However, patients who undergo these procedures may experience increased discomfort during follow-up colonoscopies. Therefore, it is essential to provide them with strategies to alleviate this discomfort [15,34,35].

Combined oral contraceptives and hormonal intrauterine devices significantly reduce the risk of both sporadic ovarian cancer and ovarian cancer associated with BRCA1 and BRCA2 mutations. Although there is a common belief that this relationship also applies to women with Lynch syndrome, current evidence is insufficient to support this assumption.

Lifestyle factors have an impact on the development of colorectal cancer in individuals with Lynch syndrome. However, no studies have confirmed a connection between lifestyle factors and ovarian cancer. Despite this, it is recommended that patients maintain a healthy diet, monitor their body weight, limit or eliminate alcohol consumption, avoid smoking, and engage in regular physical activity.

Lynch syndrome does not affect fertility. However, it is important to inform patients that the condition is caused by an autosomal dominant mutation, which carries a 50% risk of transmission to offspring. Preimplantation genetic diagnosis (PGD) followed by in vitro fertilization (IVF) can significantly reduce the risk of passing on the mutation. Although this is a complex procedure and few couples choose to undergo it, physicians should ensure that patients are aware of this option [7].

Summary:

Lynch syndrome is one of the most common hereditary syndromes predisposing individuals to cancer [36]. The risk of developing ovarian cancer is 10-17%, and it occurs in younger patients compared to those without mutations. Currently, transvaginal ultrasound (TVUS),

MRI, and markers such as CA125 and HE4 are used in diagnostics. Additionally, the RMI and ROMA indices are employed. In patients diagnosed with Lynch syndrome, it is crucial to not only conduct screening but also to implement preventive measures, such as bilateral salpingo-oophorectomy (BSO).

Although the survival rate for ovarian cancer patients with Lynch syndrome is relatively good, further research is needed to improve diagnostics and treatment.

Cancer vaccines, including those developed for ovarian cancer, may represent a breakthrough in the prevention and treatment of cancer.

DISCLOSURES

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