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CASE REPORT

Dual malignancies in Lynch Syndrome: A rare case of synchronous colorectal and ovarian cancer highlighting the potential role of immunotherapy

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ABSTRACT

We report a 35-year-old woman with dual malignancies associated with Lynch Syndrome, diagnosed with Stage IIIC sigmoid colon adenocarcinoma and Stage IIA left ovarian serous papillary adenocarcinoma. Germline testing revealed MSH2 gene mutation, particularly exon 7 deletion. This case highlights the importance of early detection, germline testing and individualized management strategies for Lynch Syndrome patients. It also underscores the potential of immunotherapy as an effective therapy for recurrent Lynch-associated cancers, emphasizing the need for continuous research into novel therapeutic modalities.

1. INTRODUCTION

Lynch Syndrome, the leading cause of hereditary colorectal cancer, arises from pathogenic variants in DNA mismatch repair (MMR) genes, which include MLH1, MSH2, MSH6, PMS2, and EPCAM [1]. Of all MMR genes, PMS2 has the highest prevalence, followed by MSH6, MLH1 and lastly MSH2 [2].

Approximately 3% of colorectal cancer and 2% of endometrial cancer cases worldwide are attributed to Lynch Syndrome [1]. Lynch-associated ovarian cancer has a much lower incidence, responsible for 0.7% cases. It is also implicated in small bowel, biliary tree, urothelial system, brain, prostate and skin malignancy [1].

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Early diagnosis is essential to allow timely interventions and eliminate possible cancer risks. Although professional guidelines for screening and treatment exist, more studies need to be carried out given the rarity of this syndrome. This case aims to investigate the genetic results, diagnostic approach, screening and prophylactic strategies, with special emphasis on the increasingly important role of immunotherapy in managing Lynch Syndrome.

2. CASE PRESENTATION

This case demonstrates a 35-year-old woman under the diagnosis of dual malignancies secondary to Lynch Syndrome. She was first diagnosed at the age of 23 with high-risk Stage IIIC sigmoid colon adenocarcinoma based on the 8th American Joint Committee on Cancer (AJCC) Cancer Staging System. Subsequently, she completed 8 cycles of adjuvant XELOX chemotherapy consisting of capecitabine (Xeloda) and oxaliplatin.

At 32 years old, she was diagnosed with Stage IIA left ovarian serous papillary adenocarcinoma based on the FIGO (International Federation of Gynecology and Obstetrics) system. She had undergone left salpingo-oophorectomy with lymph node dissection, followed by 6 cycles of carboplatin and paclitaxel chemotherapy.

Unfortunately, she experienced pelvic recurrence a year later and underwent secondary cytoreductive surgery. Following that, she received 8 cycles of oral cyclophosphamide, pembrolizumab and bevacizumab with subsequent maintenance therapy for 2 years. PET-CT (Positron Emission Tomography-Computed Tomography) after treatment showed no evaluable disease. Genetic testing later revealed a pathogenic variant in the MSH2 gene, particularly exon 7 deletion, inherited from the paternal side.

3. DISCUSSION

3.1 Pathogenesis

Lynch Syndrome is a hereditary cancer caused by germline mutations in DNA mismatch repair genes, as opposed to most sporadic neoplasms which are caused by somatic mutations. Germline mutations occur in reproductive cells before fertilization, making them inheritable and present at birth [3] . Such mutations affect all cell lines, thus causing multiple primary tumors formation [3].

Approximately 75% of colorectal cancers (CRC) are sporadic, while familial and hereditary causes account for 15–20% and 6% respectively [4]. Familial CRCs involve multigenic inheritance, where multiple genes contribute to cancer development [4]. There is no clear and validated DNA test to identify a single high-penetrance gene responsible for the cause. Therefore, risk estimates are usually based on family history and counselling focuses on broader interventions and population-level screenings. In contrast, hereditary cancers like Lynch Syndrome are monogenic, where a single mutation in one of the DNA MMR genes is sufficient to cause cancer [4]. Thus, genetic counselling can be more targeted, as family members of affected individuals have a 50% risk of inheriting the mutation. Carriers can then be informed of their increased risk of extra-colonic cancers and advised on individualized screening or prophylactic measures.

DNA MMR genes maintain genomic stability by repairing nucleotide mismatches such as erroneous insertion, deletion or duplication during DNA replication [5]. Errors are most likely to occur in microsatellites, which are stretches of short repetitive sequences [5]. Defective MMR genes secondary to Lynch syndrome result in microsatellite instability (MSI), which is characterized by the expansion or contraction of these sequences due to uncorrected mismatches [5]. This results in proliferation of aberrant microsatellites within tumor suppressor genes and proto-oncogenes, resulting in cancerous growth [1].

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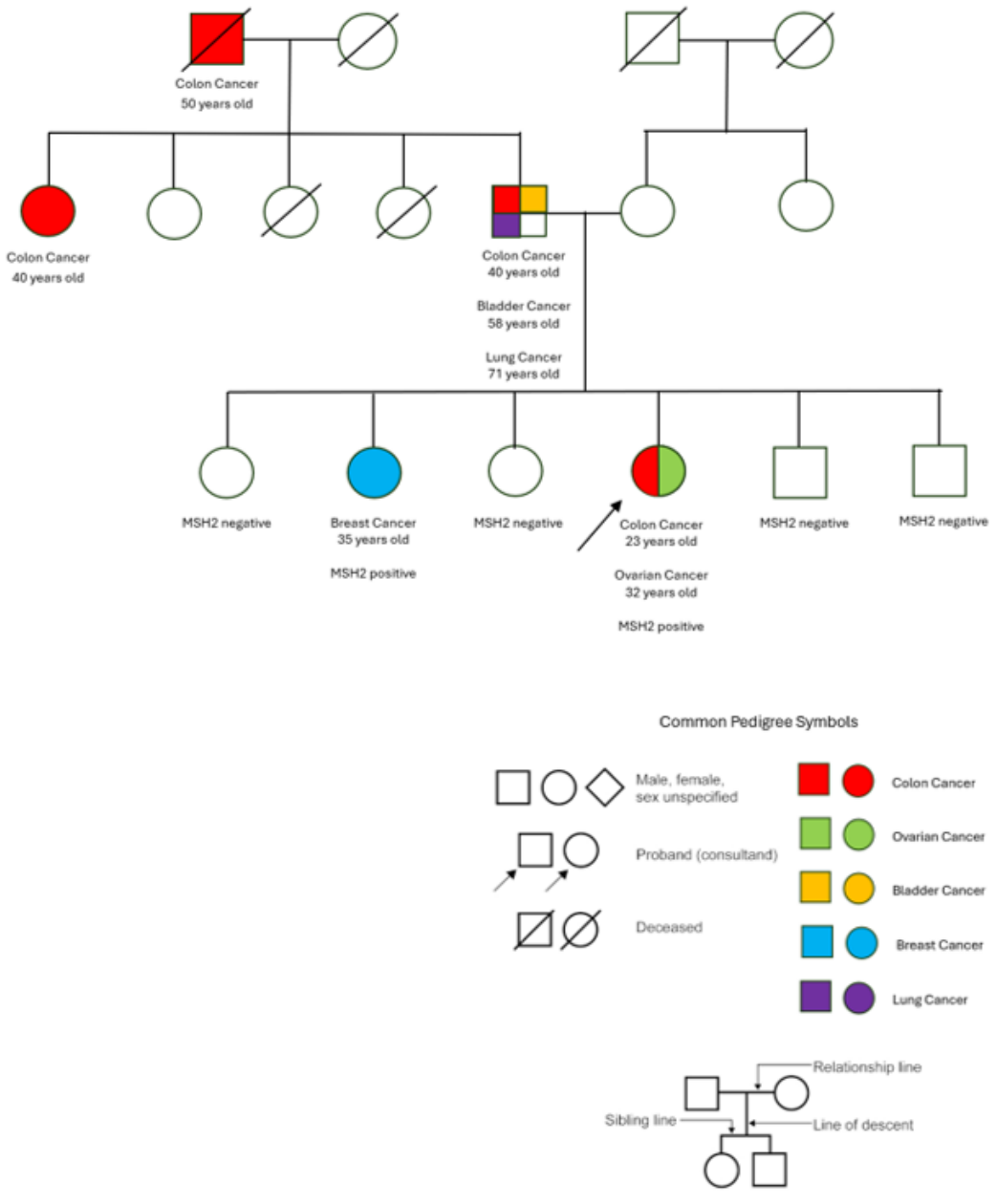

Fig. 1 Family pedigree of the patient

Source: Ng Kai Jian et al (2026)

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3.2 Genotype-phenotype correlation

The lifetime cancer risk in Lynch Syndrome varies by pathogenic variant (PV) [6]. MLH1 and MSH2 carriers have higher colorectal cancer (CRC) risks (44–53% and 42–46%, respectively) than MSH6 (12–20%) or PMS2 (3%) [7]. MSH2 also poses the highest risk for gynecological cancers, with 46% for endometrial and 17% for ovarian cancers [7]. Lifetime risk of endometrial and ovarian cancers of other pathogenic variants: MLH1 (35%, 11%), MSH6 (41%, 11%) and PMS2 (13%, 3%) respectively [6]. This patient's MSH2 mutation explains her early-onset colorectal and ovarian cancers. Her family history, including relatives diagnosed with early CRC, aligns with evidence that MSH2 mutations significantly increase CRC risk.

3.3 Diagnosis

To diagnose Lynch Syndrome, Amsterdam Criteria and Bethesda Guidelines have been introduced to identify patients at risk based on detailed family history [8]. Suspected cases should then proceed with tumor testing for microsatellite instability (MSI) or immunohistochemistry (IHC) [8]. MSI testing detects microsatellite expansion or contraction, termed "MSI-High" (MSI-H), while IHC detects the absence of MMR proteins [8].

A positive IHC or MSI-H result suggests MMR deficiency but has yet to confirm the diagnosis of Lynch Syndrome, as such tumors may arise from germline MMR pathogenic variants (PVs), biallelic somatic inactivation of MMR, or promoter hypermethylation of MLH1 in sporadic causes [1]. In Lynch Syndrome, individuals tend to inherit germline mutation from parents for one allele only, with the second allele inactivated later due to somatic mutation, loss of heterozygosity or epigenetic silencing via promoter hypermethylation [1]. In sporadic cancers, MMR gene inactivation primarily results from promoter hypermethylation, often with the presence of BRAF mutation, which does not occur in Lynch Syndrome [1].

To confirm Lynch Syndrome, patients with MSI-H tumors require genetic testing through MMR gene panel testing to identify germline mutations [7]. In cases where no germline mutation could be detected, MLH1 promoter methylation or BRAF mutation testing can help identify sporadic causes [7]. In rare instances, when all tests prove to be negative, tumor DNA sequencing to identify biallelic somatic inactivation of MMR genes may be necessary [7].

3.4 Management

Management of Lynch Syndrome patients consist of two components, screening and prophylactic strategies. In this case, the patient with MSH2 mutation presents a concerning risk for colorectal and gynecologic cancers.

Colorectal cancer (CRC) screening is recommended to begin between 20–25 years old or five years prior to the earliest family diagnosis, whichever comes first [9]. Annual or biennial colonoscopy can effectively identify and remove adenomatous polyps, reducing CRC risk [9]. Besides, the National Comprehensive Cancer Network (NCCN) and the American College of Obstetricians and Gynecologists (ACOG) recommend women aged 30 – 35 years old to undergo endometrial biopsy and transvaginal ultrasound every 1–2 years to screen for endometrial cancer [10-12]. However, routine ovarian cancer screening, like CA-125 testing or transvaginal ultrasound, has no proven efficacy in decreasing mortality and hence it is not formally recommended [8].

Prophylactic measures vary depending on cancer type and patient factors. Generally, prophylactic colectomy will not be necessary since routine colonoscopy with polypectomy can effectively prevent CRC [6]. However, in cases where CRC cannot be adequately managed with endoscopic surveillance, colectomy with ileorectal anastomosis (IRA) may be preferred, given the high risk of metachronous CRC in Lynch Syndrome patients [9]. Studies have shown that patients who had segmental resections rather than extensive

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colectomies experienced higher metachronous CRC rate of 16% at 10 years, rising to 62% at 30 years [9]. The risk of metachronous cancer is substantially reduced if extensive colectomy is performed (0–3.4%) [9]. This patient had chemotherapy for Stage IIIC sigmoid adenocarcinoma and later required an ileostomy for pelvic recurrence.

For gynecological cancers, hysterectomy and bilateral salpingo-oophorectomy (BSO) may serve as risk-reduction options to be discussed with patients in their early 40s or after childbearing [10]. While BSO negates ovarian cancer risk, early surgical menopause may lead to increased risks of osteoporosis, cardiovascular disease, as well as cognitive or sexual dysfunction [8]. Moreover, certain variants like PMS2 may not necessitate oophorectomy due to negligible gynecologic cancer risk [8]. Therefore, NCCN recommends that the decision to have BSO should be individualized based on completion of childbearing, menopausal status, medical comorbidities and specific pathogenic variants [8].

This patient underwent left salpingo-oophorectomy and chemotherapy, preserving her fertility and hormonal function. Hysterectomy and right salpingo-oophorectomy may be considered in the future, particularly as she approaches her 40s while considering various factors mentioned above.

Previously, treatment for sporadic and Lynch-associated colorectal, endometrial, and ovarian cancers was the same, regardless of Lynch status. Recent studies have demonstrated classic findings of dense T-lymphocytes infiltration and cytokine-rich microenvironment which mounts antitumor immune activity in MMR-deficient tumors [13]. Concurrently, high expression of immune checkpoint ligands, including PD-1 and PD-L1, which allows tumours to evade immune attacks have been observed within the same microenvironment [13]. These recent insights have led to the development and application of Pembrolizumab, an anti–PD-1 antibody, which blocks these immune checkpoints, reactivating cytotoxic T-cell responses [13]. This explains why MMR-D tumors, including those linked to Lynch syndrome, respond better to immunotherapy than to traditional chemotherapy [14].

While immunotherapy is not yet the standard of care for Lynch-associated cancers due to limited studies in this population, emerging evidence supports its use in recurrent or progressive MMR-deficient endometrial and ovarian cancers [15]. In fact, Pembrolizumab, was the first drug granted accelerated FDA approval for a tumor-agnostic indication, approved for all non-colorectal, MMR-deficient/MSI-H tumors [15]. The largest research to date, KEYNOTE-158, enrolled 233 patients with advanced MSI-H/MMR-deficient non-colorectal cancers who had failed previous interventions [15]. Among 27 tumor types, endometrial and ovarian cancers contributed to 49 and 15 cases respectively [15]. The objective response rate (ORR) defined as ≥30% tumor reduction without disease progression was 34.3% [15]. Overall, 57.1% experienced some tumor shrinkage, with 44.2% had reductions of ≥30% [15]. Particularly, among 47 patients with endometrial cancer, 70% (37 patients) had tumor reductions >30%, highlighting the potential of immunotherapy in this subgroup [15].

Combining immune checkpoint inhibitors with antiangiogenics like bevacizumab enhances effectiveness of immunotherapy. Tumors produce vast amounts of proangiogenic factors like VEGF which promote chaotic vasculature and hypoxia, further creating an immunosuppressive microenvironment [16]. Excessive VEGF may also reduce cytotoxic T-cell proliferation, increase PD-L1 expression by tumors, and promote endothelial dysfunction which impedes immune cells infiltration [16]. Therefore, antiangiogenics works by blocking VEGFs to ensure transient normalization of the chaotic tumor vasculature, improving oxygenation and immune cell infiltration [16]. They may also downregulate PD-L1 expression, producing synergistic effects with immune checkpoint inhibitors [16].

Metronomic oral cyclophosphamide enhances antitumor immunity by depleting regulatory T cells, complementing VEGF inhibition and PD-1 blockade [17]. In a cohort of 40 women with recurrent ovarian cancer, including platinum-resistant cases, the combination of pembrolizumab, bevacizumab, and cyclophosphamide showed an ORR of ~47%, clinical benefit in 95%, and durable responses (>12 months) in 25% of patients [17]. These promising results offer us an effective future treatment strategy for recurrent ovarian cancer.

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The patient was treated with maintenance pembrolizumab and bevacizumab for two years following a pelvic recurrence. Although the recurrence occurred within one year—typically suggestive of platinum sensitivity—platinum rechallenge was avoided due to the potential risk of cumulative neurotoxicity. More significantly, the identification of MSH2 mutation confirmed Lynch syndrome and MMR-deficiency, indicating a high likelihood of response to immune checkpoint inhibitors. The addition of cyclophosphamide and bevacizumab was intended to synergize with immunotherapy by modulating the tumor microenvironment and enhancing immune activation. Her most recent PET-CT showed no evaluable disease, demonstrating excellent response to the immunotherapy regimen.

4. CONCLUSION

In conclusion, this report emphasizes the importance of early detection and individualized management in Lynch Syndrome patients, particularly those with dual malignancies. Continuous genetic counselling coupled with regular screenings for patients and their families remains essential to reduce future cancer risks and guide further management. The patient's positive response to immunotherapy has proven its potential efficacy for recurrent Lynch-associated cancers. This case adds to the growing evidence for personalized treatment strategies in Lynch Syndrome, especially with novel therapeutic modalities like immunotherapy.

5. CONFLICT OF INTEREST

Author declares none.

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