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Case Presentation

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Quintuple Primary Malignancies in Lynch Syndrome: A Case Report and Literature Review

Chen Zhenyun[1], Feng Shuai[2], Li Xiaohong[1], Zhang Xiaohong[3], Niu Hongpeng[1] and Li Dapeng[2*]

[1]The first Department of Gynecology, Linyi tumor Hospital, Shandong, 276000, China

[2]Department of Gynecologic Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China

[3]Department of Pathology, Linyi tumor Hospital, Shandong, 276000, China

[*]**Corresponding author**: Li Dapeng, Department of Gynecologic Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jiyan road 440, Huaiyin District, Jinan, Shandong, CN 250000, China, Tel: 15553115531; Fax: 0531-67626961; E-mail: dpli@sdfmu.edu.cn

Abstract

Case: This article presents a rare clinical case of a 45-year-old female with six metachronous tumors during the period from 2010 to 2020 (over 10 years). Five primary malignancies show mismatch repair gene defection. No other cases of five colon and extracolonic primary malignancies in patient with Lynch syndrome have been reported in literature.

Outcome: The patient underwent four surgeries and multiple courses of chemotherapy and diagnosed with Lynch syndrome according to family history and genetic testing.

Conclusion: Lynch syndrome with extracolonic malignancies (stomach, endometrial, ovarian, renal, small bowel, hepato-biliary tract, urinary tracts) as the first manifestation was difficult diagnosed timely. Patients who present with multiple malignancies from independent locations should be considered to identify any underlying hereditary cancer syndromes.

Keywords: Lynch syndrome; Multiple malignancies; Metachronous cancer

Introduction

Lynch Syndrome (LS) is a cancer predisposing genetic disease mediated by pathogenic mutations in DNA Mismatch Repair (MMR) genes MLH1, MSH2, MSH6, and PMS2. It is characterized by MSI and a loss of expression of

MMR proteins [1]. As a result of mutation in DNA mismatch repair genes, various cancers risk increased and occurred at earlier age, such as colorectal, endometrial, ovarian, renal, small bowel, urinary tracts, hepato-biliary tract, breast cancer) [2-5]. CRC is the most common cancers in LS, and the lifetime risks of CRC at 70 years old for MLH1 and MSH2 gene mutation carriers ranged from 40% to 52%. But for patients with MSH6 and PMS2 gene mutations, the cumulative lifetime risks for CRC were lower [6]. MSH2 and MSH6 are more closely related to the incidence of endometrial carcinoma. Endometrial cancer is the most common extra intestinal sentinel cancer caused by germ line Pathogenic Variants (PVs) in MMR genes [7]. LS-associated Endometrial Cancer (LS-EC) has specific clinicopathological features such as early age of onset, endometrioid carcinoma, and lower uterine segment involvement. And LS-EC has an intermediate prognosis according to the molecular classification and has a good response to immunotherapy [8]. Histopathology of LS cancers show more poorly differentiated, but LS cancers are less likely to metastasize. Diagnosis of LS is often underestimated and ignored, especially for extra intestinal cancers [9]. Amsterdam criteria and Bethesda Guidelines are most commonly used in identifying patients with a high risk of being affected by LS. But the screening and diagnosis criteria's of LS are controversial. Combination of MMR-Immunohistochemistry (IHC), MSI-analysis and targeted MLH1-methylation testing can identify patients with LS [10]. This article presents a rare clinical of a 45-year-old female diagnosed as Lynch syndrome with five colon and extracolonic primary malignancies during the period from 2010 to 2022 (over 12 years). No quintuple primary malignancies in patient with Lynch syndrome have been reported in past literature.

Case Presentation

General information

The patient was a 45-year-old female who underwent "radical right mastectomy + right axillary lymph node dissection" on November 11, 2010 for "right breast mass" and postoperative pathology: right breast invasive ductal carcinoma **(Figure 1).** Postoperative diagnosis: right breast cancer p-T4N0M0. Six cycles of postoperative intravenous chemotherapy were administered with a regimen of cyclophosphamide + adriamycin + tegafur. Oral toremifene 40 mg qd was administered for 5 years after chemotherapy. On May 25, 2015, she underwent "enlarged resection of right submandibular gland mass + facial nerve dissection + right cervical lymph node dissection" for "right submandibular gland mass", and the postoperative pathology: (right submandibular gland) malignant change of pleomorphic adenoma, malignant change of ductal carcinoma, invasion of the nerve bundle; postoperative examination of 2/22 lymph nodes showed cancer metastasis **(Figure 1).** Postoperative diagnosis: right submandibular gland carcinoma T4N1M0. Postoperative intensity-modulated radiotherapy was performed in the right submandibular gland area and cervical lymph node area, P-GTV 66Gy/30f, PTV1 60Gy/30f, PTV 50.96Gy/28f. On March 10, 2016, she was admitted to the hospital for "right upper abdominal distension and discomfort for 7 months, ascending colonic mass was found for 5 days "Postoperative pathology: (colon) bulging type hypofractionated mucinous adenocarcinoma, invasion of the fibrous epithelium, nerve invasion (+), no definite choroidal carcinoma thrombus was seen **(Figure 1).** MLH1 (-), PMS2 (-), MSH2 (+), MSH6 (+). Postoperative diagnosis: pT4N0M0 cancer of the colon and liver area. 6 cycles of postoperative intravenous chemotherapy with

oxaliplatin + capecitabine. On August 5, 2020, she was admitted to the hospital with "lower abdominal distension for 1 month and pelvic mass for 1 day".

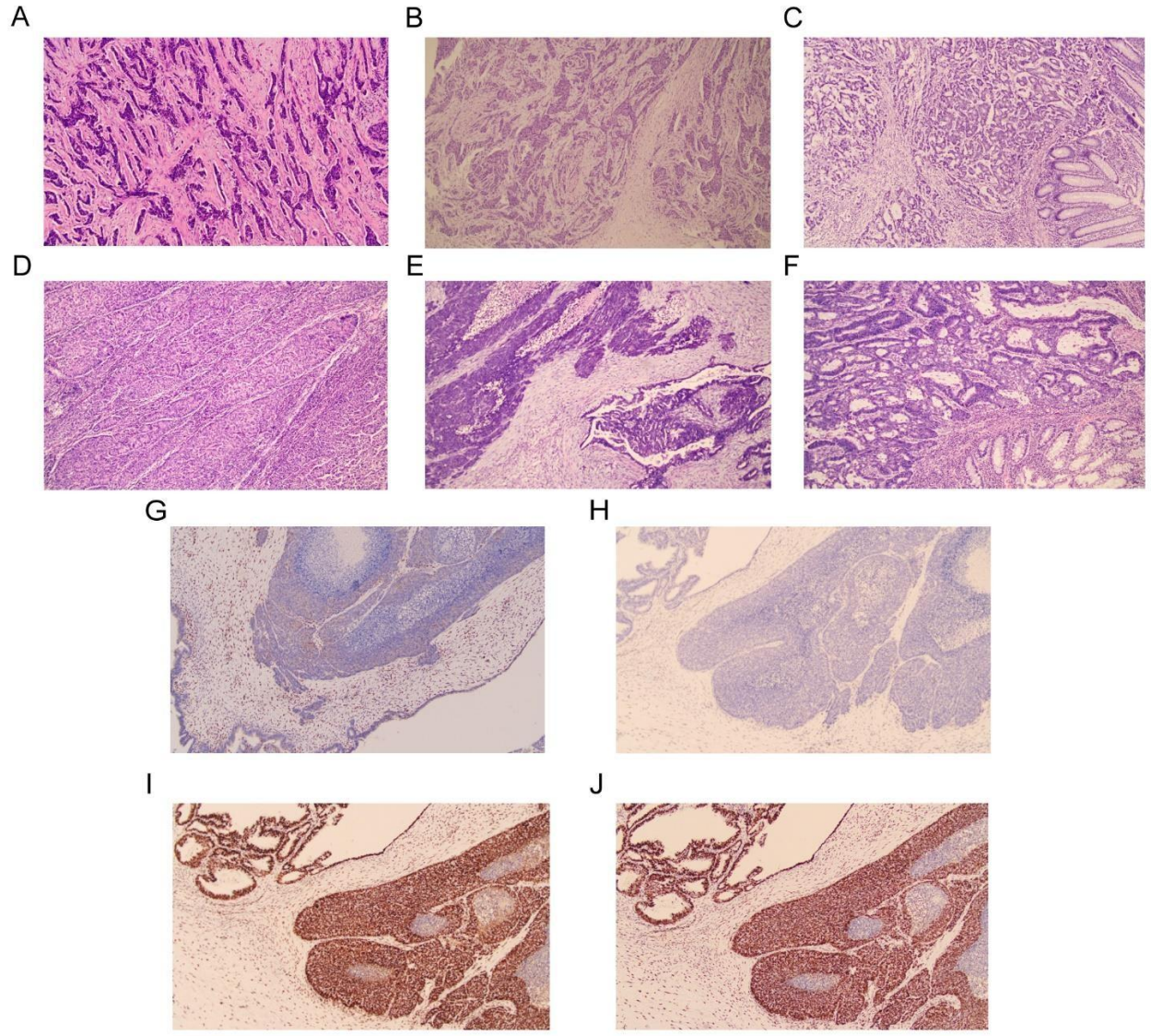

Figure 1: Postoperative pathology. A: Right breast: invasive ductal carcinoma (HE ×100). B: Right submandibular gland: ductal carcinoma (HE ×100). C: Ascending colon: moderately differentiated mucinous adenocarcinoma (HE ×100) D: Uterus: highly differentiated endometrioid adenocarcinoma (HE ×100). E: Ovary: poorly differentiated endometrioid adenocarcinoma (HE ×100). F: Splenic flexure of the colon: moderately differentiated adenocarcinoma (HE ×100). G: Immunohistochemistry of endometrioid adenocarcinoma MLH1(-) (IHC ×100). H: Immunohistochemistry of endometrioid adenocarcinoma PMS2(-) (IHC ×100). I: Immunohistochemistry of endometrioid adenocarcinoma MSH2(+) (IHC ×100). J: Immunohistochemistry of endometrioid adenocarcinoma MSH6(+) (IHC ×100).

Physical examination

A transverse incision scar of about 10 cm in length was seen under the right jaw and a longitudinal incision scar of about 6 cm in length was seen in the right middle and lower neck; the right breast was absent and showed postoperative changes; a longitudinal incision scar of about 16 cm in length was seen in the right side of the epigastrium; gynecological examination: the diameter of the cervix was about 4 cm, hard, and the uterus was the size of a 3-month pregnancy; masses are found in the bilateral adnexal area, about 9 cm × 8 cm × 8 cm on the right side and about 6 cm × 5 cm × 5 cm on the left side, irregular, cystic, and movable.

Adjuvant examination

Intensive CT of the abdominopelvic cavity showed: multiple cystic masses in the abdominopelvic cavity and left adnexal area, with uneven intensification in the solid part and internal segregated intensification, with the larger one measuring about 85 mm×72 mm. The endometrium was significantly thickened and intensified, with fluid and birth control ring visible in the uterine cavity, and no enlarged lymph nodes were seen in the retroperitoneum. Colorectal microscopy showed a 2.5 cm × 3.0 cm bulging mass in the splenic region of the colon 40 cm from the anus, and tissue was taken and sent for pathology: adenocarcinoma; cervical biopsy: chronic cervicitis; diagnostic scraping pathology: endometrial adenocarcinoma.

Treatment

On August 18, 2020, the exploratory laparotomy was performed under general anesthesia, and the intraoperative investigation revealed the following: about 1000 ml of brown ascites was seen in the abdominopelvic cavity, no abnormalities were detected in the liver, gallbladder, pancreas and spleen, no obvious enlarged lymph nodes were detected in the retroperitoneum of the abdominopelvic cavity, part of the small intestine was adhered to the abdominal wall, the intestinal canal was thickened in the spleen area of the colon, and a mass could be found in the intestinal canal, which was hard and about 4 cm in diameter. The uterus was enlarged to the size of the third trimester of pregnancy, and a tumor was seen in each ovary bilaterally, the right side was about 7 cm×8 cm×8 cm in size, with a rupture on the surface; the left side was about 5cm×5cm×4cm in size, with a smooth surface; the greater omentum and appendix were missing. According to the intraoperative exploration, pelvic adhesion release + subextensive hysterectomy + bilateral adnexal resection + abdominal and pelvic lymph node dissection + partial descending colectomy + intestinal anastomosis were given. Postoperative pathology: (right adnexa) hypofractionated endometrioid adenocarcinoma of ovary, tumor size: 9 cm×7 cm×5 cm size; (left adnexa) junct ional endometrioid tumor of ovary with malignant part of moderate-low differentiated adenocarcinoma, tumor size: 6 cm×5 cm×5 cm; (uterus) endometrial complex hyperplasia with atypical hyperplasia, part of malignant change to highly differentiated endometrioid adenocarcinoma, tumor size. 3 cm×2.5 cm×2 cm, no invasion of muscle layer, no definite choroidal carcinoma thrombus and nerve invasion; ER(2+) PR(2+); 25 abdominopelvic lymph nodes were not found to be cancerous. (The tumor size was 4 cm×3.5 cm×2 cm, invading less than 1/2 layer of muscle layer, no definite vascular and nerve invasion; no cancer was detected in 4 lymph nodes at both cut edges and perianal area

(Figure 1). CK20 (+), Villin (+), CDX2 (+), CK7 (-) MLH1 (-), PMS2 (-), MSH2 (+), MSH6 (+) Ki67 (~70%) **(Figure 1G-J).** Based on the patient's immunohistochemistry, the possibility of Lynch Syndrome (LS) was considered not to be excluded. After communication with the pathology department, immunohistochemistry of the patient's breast was added: MLH1 (+), PMS2 (+), MSH2 (+), MSH6 (+). Immunohistochemistry of submandibular gland: MLH1 (-), PMS2 (-), MSH2 (+), MSH6 (+). The patient was given hereditary tumor 45 gene test (Nantong Zhongke Medical Laboratory): the patient carried MLH1 gene c.1409+1G>A heterozygous variant with shear mutation type, which may cause disease. Postoperative diagnosis: stage Ic ovarian cancer, stage Ia endometrial cancer, pT2N0M0 cancer in the splenic region of the colon, postoperative treatment with paclitaxel + cisplatin + PD-1 inhibitor for 6 cycles and continued with PD-1 inhibitor (carrilizumab 3 mg/kg, once every 3 weeks) for maintenance treatment until 1 year. This patient was diagnosed as Lynch syndrome and five colon and extracolonic primary malignancies were mismatch repair gene defect. Right breast cancer was not related to LS (Table 1).

Table 1: Medical history.

Year	Age at diagnosis	Localization	Operation	Stage	Tumour grade	MSI
2010	33	Right mastectomy	radical right mastectomy +right axillary lymph node dissection	T4N0M0	G3	MLH1
						(+)
						PMS2
						(+)
						MSH2
						(+)
						MSH6
						(+)
2015	38	Submandibular gland	enlarged resection of right submandibular gland mass + facial nerve dissection + right cervical lymph node dissection	T4N1M0	G3	MLH1
						(-)
						PMS2
						(-)
						MSH2
						(+)
						MSH6
						(+)
2016	39	Ascending	radical right hemicolectomy	T4N0M0	G3	MLH1

		colon				
						(-)
						PMS2
						(-)
						MSH2
						(+)
						MSH6
						(+)
2020	43	Left ovary	salpingo- oophorectomy	T1c2N0 M0	G2-3	MLH1
						(-)
						PMS2
						(-)
						MSH2
						(+)
						MSH6
						(+)
2020	43	Endometrium	Modified radical hysterectomy	T1N0M0	G1	MLH1
						(-)
						PMS2
						(-)
						MSH2
						(+)
						MSH6
						(+)
2020	43	Descending colon	Partial descending colectomy	T2N0M0	G1	MLH1
						(-)
						PMS2
						(-)
						MSH2
						(+)
						MSH6
						(+)

Follow-up status

The patient is generally in good condition with no signs of recurrence at 4-month follow-up.

Genetic counseling

We conducted genetic counseling to the patient and drew a family map **(Figure 2).** 10 was the prob and with primary breast, submandibular, ascending colon, ovarian, endometrial, and colonic splenic region cancers. Grandpa **[1]** died at the age of 62 and grandma **[2]** died at the age of 90, and the cause of death is unknown. One uncle **[3]** died at the age of 5 and the cause of death is unknown. Another uncle **[4]** died of laryngeal cancer at the age of 71. One aunt **[5]** died of colon cancer at the age of 65. Another aunt **[6]** died at the age of 38, and the cause of death is unknown. Her mother **[7]** has colon cancer, father **[8]** is healthy. Her brother **[9]** and son **[12]** are in good health.

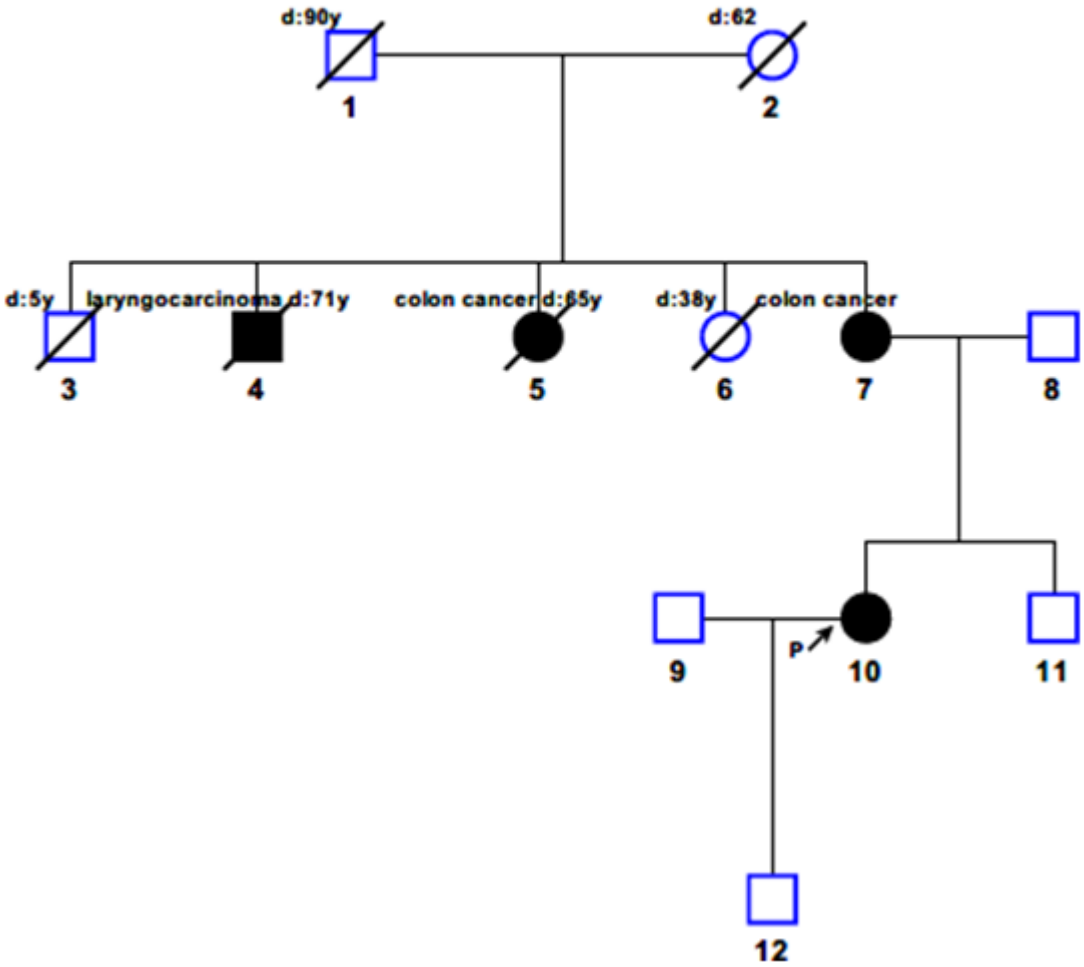

Figure 2: Family Lynch Syndrome.

Discussion

Patients with LS have a significantly higher risk of developing multiple cancers, including rectal cancer, endometrial cancer, gastric cancer, ovarian cancer, pancreatic cancer, ureteral cancer, renal pelvis cancer, neurological tumors (keratoblastoma), small bowel cancer, sebaceous gland cancer, and keratoacanthoma **[11],** which can occur either simultaneously or sequentially, but cases of multiple tumors occurring in the same patient are relatively rare. This article reports a patient with LS-associated sequential and/or concurrent primary breast, submandibular, ascending colon, ovarian, endometrial, and colonic splenic region cancers. The patient had breast cancer, submandibular gland cancer and ascending colon cancer, but did not pay enough attention to them and was not diagnosed with LS as early as possible. Until she came to our gynecology department for the fourth time due to "pelvic mass". The pathological

and immunological combinations can indicate that they are independent cancers. Postoperatively, based on molecular pathology and immunohistochemistry, together with the patient's past and family history, LS was considered and the patient was given a genetic tumor 45 gene test: the patient carries MLH1 gene c.1409+1G>A heterozygous variant, the type of variant is shear mutation, which may cause disease. The MLH1 gene c.1409+1G>A variant is a classical shear mutation with no record of population carriage. Due to the lack of prior knowledge of LS, for this case, the diagnosis of LS was neglected upfront during the consultation. It was not until the patient's 4th surgery that LS was considered based on immunohistochemistry, further pursued past and family history, and genetic testing was given to confirm the diagnosis with additional immunohistochemistry for 6 different sites of primary tumors, 5 of which had immunohistochemistry for MLH1 and PMS2 expression deficiency, and only breast pathology immunohistochemistry results of MLH (+), PMS2 (+), MSH2 (+), and MSH6 (+). Communication with the pathologist, combined with the patient's medical history and age of onset, maybe the true immunohistochemical results were affected by the long duration of the specimen or other pathogenic genes could cause the breast cancer. Therefore, early diagnosis of LS is very important, and in the context of this case, if immunohistochemistry and combined with genetic testing can confirm the diagnosis earlier after performing breast and submandibular carcinoma, annual imaging, gastroscopy, diagnostic curettage, and hematological tumor markers may be able to stop the tumor during subsequent follow-up. Recent findings show that MMR status correlates with anti-PD-1 immunotherapy in advanced cancer, and anti-PD-1 immunotherapeutic agents are efficacious in solid tumors with MMR gene mutations **[12].** The patient in this case had primary breast cancer, submandibular gland cancer, ascending colon cancer, endometrial cancer, ovarian cancer, and cancer of the spleen region of the colon. Immunohistochemistry was inconclusive for MLH1 and PMS2 expression deficiency for breast cancer, which was a 10-year-old specimen. MSI-H and/or dMMR showed in all other cancers. The patient refused to continue radiotherapy due to multiple surgeries and radiotherapy and chosen PD-1 inhibitors. The patient is in good general condition and is able to take care of herself, with no signs of recurrence or other sites of tumor recurrence. With the increasing number of reported cases and the development of molecular pathology, LS is gradually gaining attention, especially in "colorectal, endometrial and ovarian cancers". However, in the diagnosis of LS, neither the Amsterdam II nor the Bethesda criteria can confirm the diagnosis as early as possible, and genetic testing is required to confirm the diagnosis, but genetic testing is expensive. There is still a lack of convenient, effective and economical screening methods for early LS screening, and there is a lack of large clinical data to support the prevention and treatment of LS, which are worth exploring in the future on the road of fighting against tumors.

Informed Consent Statement

All investigations on human subjects have been subject to patient consent and patient anonymity was preserved.

Disclosures

The authors declare that they have no conflict of interest. The specimens were used with informed consent from the patient.

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