

Diaphragmatic clear cell carcinoma with Lynch syndrome after surgery for atypical endometrial hyperplasia and ovarian endometriosis: A case report

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Abstract. Clear cell carcinoma (CCC) of the diaphragm is rare, with an origin that is reported to be associated with malignant transformation of extraperitoneal endometriosis. Lynch syndrome (LS) is an autosomal dominant hereditary cancer syndrome caused by germline pathogenic variants in one of the DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2*. Women with LS have a significantly increased lifetime risk of endometrial and ovarian cancer. CCC is a common histology of endometriosis- and LS-associated malignancy. The present study describes the case of a 51-year-old woman with an intra-abdominal mass found during a routine physical examination. The patient had undergone total hysterectomy and bilateral adnexectomy for atypical endometrial hyperplasia (AEH) and ovarian endometriosis, respectively, 3 years previously. Enhanced computed tomography showed a mass on the surface of the liver. Laparoscopic examination of the abdominal cavity revealed a tumor on the underside of the right diaphragm, which was then surgically excised. Pathological examination of the excised tumor, along with immunohistochemistry, led to a diagnosis of CCC. Since LS was suspected due to the genetic family history of the patient, microsatellite instability analysis was performed on the diaphragmatic

tumor, and the results were positive. Immunohistochemistry was performed for MMR proteins in AEH and CCC cells, both of which revealed loss of MSH2 and MSH6 expression. Following detailed genetic counseling, genetic testing of MMR genes was performed, revealing a germline pathogenic variant in *MSH2* (c.1000C>T, p.Gln344*), thus confirming the diagnosis of LS. To the best of our knowledge, this is the first case report of concurrent diaphragmatic CCC and LS. Patients with LS and endometriosis are at risk of developing ovarian cancer or intra-abdominal malignant tumors. In addition, immunohistochemistry screening for MMR proteins should be considered in patients with AEH and a family history of LS-related cancer, to enable early clinical intervention in cases of endometrial cancer.

Introduction

Clear cell carcinoma (CCC) in the diaphragm is extremely rare and, to the best of our knowledge, only four cases have been reported in the worldwide literature (1-4). The origin of CCC is reported to be associated with malignant transformation of extrapelvic endometriosis (1,2). Endometriosis is defined as the histological presence of endometrial glands and stroma outside the uterine cavity (5). Endometriosis typically occurs in the pelvic cavity, affecting areas such as the ovaries, uterosacral ligaments, and pouch of Douglas. However, it can also develop in extra-gonadal sites, including the abdominal peritoneum, diaphragm, lungs, pleura, bowel, ureter, and brain. While most cases of endometriosis remain benign, malignant transformation, while rare, can occur, with an estimated incidence of up to 1%. It most frequently involves the ovaries, which account for approximately 80% of endometriosis-associated malignancies (6). The most common histological types of endometriosis-associated malignancies are endometrioid carcinoma and CCC (7).

Lynch syndrome (LS), an autosomal dominant hereditary cancer syndrome, results from germline pathogenic variants (PVs) in the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or *EPCAM* gene. Colorectal cancer and endometrial cancer (EC) are the most common

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Abbreviations: AEH, atypical endometrial hyperplasia; CCC, clear cell carcinoma; EC, endometrial cancer; EH, endometrial hyperplasia; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability; OC, ovarian cancer; PV, pathogenic variant

Key words: CCC, diaphragmatic tumor, LS, endometriosis, malignant transformation, AEH

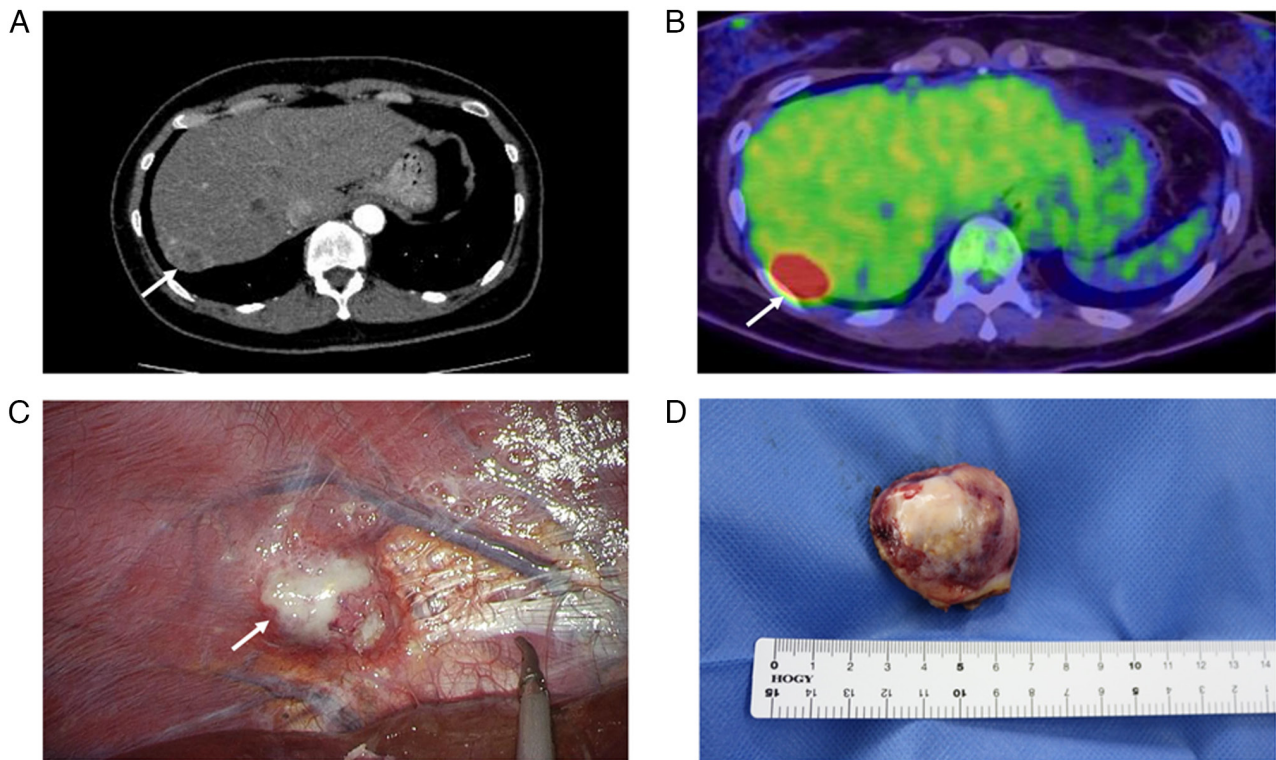


Figure 1. Imaging findings. (A) Enhanced CT showed an enhanced round mass at the limbus of the right hepatic lobe (arrow). (B) PET/CT showed accumulation of FDG at the site corresponding to the mass in (A) (arrow). Malignant tumor of hepatic or peritoneal origin was considered in the differential diagnosis. (C) Laparoscopic examination revealed a tumor on the right diaphragm (arrow). (D) Macroscopic examination revealed a solid and flat tumor of 4.1x3.8 cm. CT, computed tomography.

malignancies in LS, with lifetime risks of 53-82 and 25-60%, respectively (8,9). Notably, approximately half of women with LS develop EC as their first cancer (8,9). Endometrial hyperplasia (EH) is a disordered proliferation of epithelial cells and endometrial glands, and represents a precursor lesion to EC. The rate of progression to EC has been reported to be 1-5% in EH patients without atypia, and increases to nearly 25% in those with atypical EH (AEH) (10). Ovarian cancer (OC) is also associated with LS. The incidence of OC in women with LS accounts for 0.9-2.7% of all OC cases, with a cumulative lifetime risk of 6-17% (11). LS-related OC is known to be associated with endometrioid carcinoma and CCC histological types (12).

We herein present a clinical case of diaphragmatic CCC with LS that occurred after surgery for AEH and ovarian endometriosis.

Case report

A 48-year-old woman with abnormal genital bleeding was referred to Fukushima Medical University Hospital (Fukushima, Japan) in October 2017 from a gynecological outpatient clinic. She was diagnosed as having AEH, and underwent total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Since the bilateral ovaries were grossly normal at the first surgery, there was no rupture of the ovarian cyst. Pathological examination revealed AEH of the endometrium and endometriosis in the bilateral ovaries.

At the age of 51 years, an intra-abdominal mass was found during a routine physical examination. The patient

visited a nearby general hospital, where an enhanced computed tomography scan revealed a mass on the surface of the liver (Fig. 1A). She was referred to our hospital for surgery. The laboratory examination showed CA125: 69 U/ml (normal <35). Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography showed a mass with fluorine-18 fluorodeoxyglucose accumulation at the right hepatic lobe margins, which was suspicious for malignancy (Fig. 1B). Laparoscopic examination of the abdominal cavity revealed a tumor on the underside of the right diaphragm, which was subsequently removed laparoscopically (Fig. 1C).

Macroscopic examination showed a solid and flat tumor of 4.1x3.8 cm which had a whitish cut surface (Fig. 1D). Histopathologically, the diaphragmatic tumor was not composed of typical tubular cysts or papillary structures, but mostly showed a solid pattern (Fig. 2A). Tumor cells showed proliferation of markedly pleomorphic cells with abundant pale cytoplasm, enlarged nuclei and prominent nucleoli (Fig. 2A). Immunohistochemistry (IHC) revealed that the tumor cells were positive for CK7, HNF1B and AE1/3 (Fig. 2B-D). Expression of AFP, CD117, hCG, PLAP, S-100, ER, PgR, CK20, CK5/6, p63, Glypican3, Hepa-1, D2-40, GATA3, OCT3/4 and EBER-1 in the tumor cells was negative. Hence, the morphologic findings and the immunohistochemical profile were consistent with the diagnosis of diaphragmatic CCC of the ovary (13). The patient received six courses of adjuvant combination chemotherapy with paclitaxel and carboplatin. At the time of writing, her CA125 has returned to normal level, and

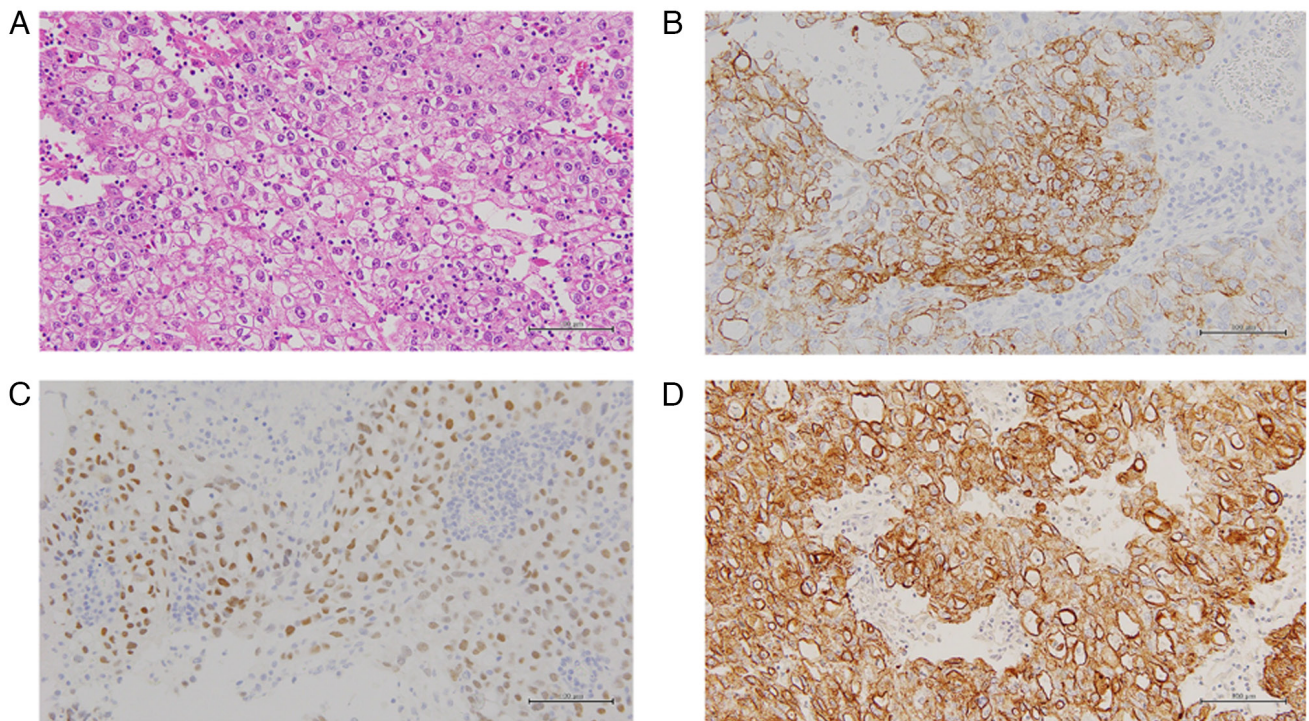


Figure 2. Pathological findings. (A) Hematoxylin and eosin staining (x200) showed proliferation of markedly pleomorphic cells with abundant pale cytoplasm, enlarged nuclei and prominent nucleoli. (B) Immunohistochemistry (x200) was positive for CK7. (C) Immunohistochemistry (x200) was positive for HNF1B. (D) Immunohistochemistry (x200) was positive for AE1/3.

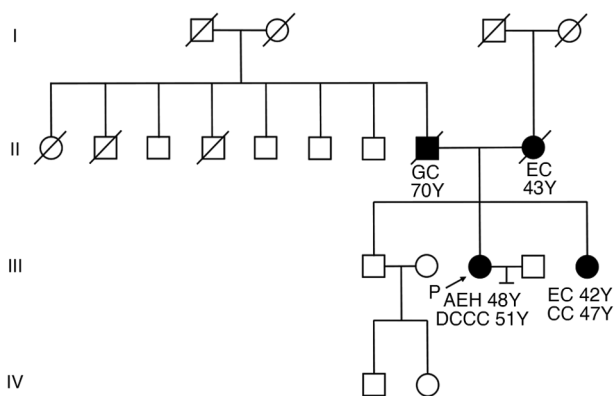


Figure 3. Family tree of the present case. The arrow indicates the proband. Numbers indicate age at diagnosis. AEH, atypical endometrial hyperplasia; DCCC, diaphragmatic clear cell carcinoma; EC, endometrial cancer; GC, gastric cancer; CC, colon cancer.

she is alive without evidence of CCC recurrence 30 months after the surgery.

Given the family history of young-onset colorectal cancer and EC, LS was suspected (Fig. 3). Therefore, microsatellite instability (MSI) analysis was performed on the diaphragmatic tumor, and the results were positive. IHC for MMR protein was performed as described previously, with primary antibodies against MLH1 (ES05, 1:50, Dako), MSH2 (FE11, 1:50, Dako), MSH6 (EP49, 1:200, Dako), and PMS2 (EP51, 1:50, Dako) (14). Both tumor cells exhibited reduced *MSH2* and *MSH6* expression (Fig. 4). Following detailed genetic counseling, genetic testing of MMR genes was performed, revealing a germline PV in *MSH2* (c.1000C>T, p.Gln344*),

which confirmed the diagnosis of LS. Her sister had early-onset endometrial and colon cancers associated with LS (Fig. 3). Although LS is inherited in an autosomal dominant manner, with a 50% chance of inheritance in first-degree family members, the relatives of the patient in the present case have not, at the time of writing, requested genetic testing for single-site *MSH2* analysis.

Discussion

Primary tumors of the diaphragm are uncommon. A previous review found that approximately 200 primary cases of diaphragmatic tumors have been reported (15). Moreover, metastases, including benign lesions such as endometriosis, as well as malignant lesions from cancers such as lung cancer, malignant mesothelioma and OC, can occur in the diaphragm (16). Diaphragmatic endometriosis occurs in 1.5% of surgically treated endometriosis patients (17). Endometriosis-related malignancy is associated with the development of CCC and endometrioid carcinoma. To date, there have been only Japanese case reports, including the present case (1-4). The prevalence of ovarian CCC differed by region and is higher in Asian populations than in Western countries (18). In particular, a recent Japanese study has reported that ovarian CCC is increased significantly, accounting for up to 30% of epithelial OC (19). The causes of difference are not clear, although one reason could be that endometriosis is more common in women of Asian origin than in Western countries (20). In addition, endometrioid carcinoma in the diaphragm associated with endometriosis has also been reported only in two cases (21,22). Matsuki *et al* reviewed cases of CCC in the peritoneum and diaphragm, and reported

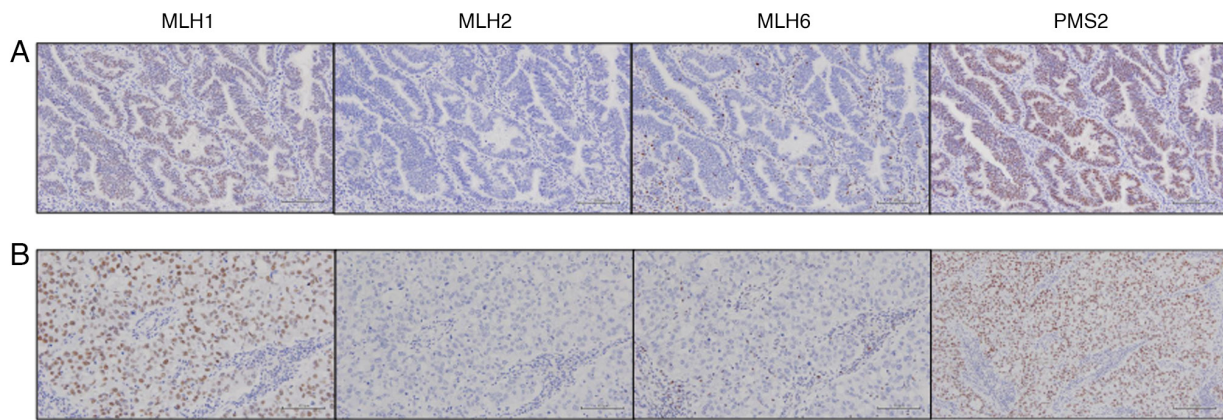


Figure 4. Immunohistochemistry (x200) for mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2). MSH2 or MSH6 expression was not observed in (A) atypical endometrial hyperplasia or (B) diaphragmatic clear cell carcinoma.

that 40% (6/15) of the patients had a history of, or currently had, endometriosis or adenomyosis (1). In 1925, Sampson defined three criteria for the diagnosis of malignant transformation of endometriosis: i) Demonstration of endometriosis within the tumor; ii) absence of other primary tumors; and iii) histological appearance consistent with an endometrial origin (23). Furthermore, in 1953, Scott added a fourth criterion: iv) morphologic demonstration of benign endometriosis contiguous with the malignant tissue (24). In the present case, previous surgery had revealed ovarian endometriosis, but there was no histological evidence of endometrial tissue near the diaphragmatic tumor. One possible explanation is that any endometrial implants originally present had undergone complete malignant transformation into a cancerous lesion. According to a previous report, endometriosis was present in the transition zone in only 36–42% of patients with malignant extraovarian endometriosis (25).

Although the molecular mechanisms for the malignant transformation of endometriosis are unknown, a review described inflammatory responses, oxidative stress and genomic aberrations as risk factors (26). MSI is a major phenotype of genomic instability in cancer, and is caused by a deficiency of the DNA MMR genes associated with LS. In recent studies, loss of MMR proteins was identified even in normal cells, including crypt foci and endometrial glands in women with LS (27,28). In the present case, decreased expression of MSH2/MSH6 and MSI-high were detected in the diaphragm tumor, although there was no coexisting endometriosis. In Western countries, the histological subtype of OC with MMR deficiency has been reported in 0.3% of serous cases, 12.5% of endometrioid cases, 3.0% of CCC cases, 0.7% of mucinous cases and 7.3% of mixed cases (29). Chui *et al* reported that all LS-OCs were either pure endometrioid carcinoma (14 cases), mixed carcinoma with an endometrioid component (four cases), or CCC (two cases), and no high-grade or low-grade serous or mucinous carcinomas were identified (30). Endometrioid carcinoma and CCC are also common pathological types of endometriosis-associated OCs. The mean interval between the last surgery and the diagnosis of CCC of the abdominal wall was reported to be approximately 21 years, indicating indolent tumorigenesis (31,32). The patient in the current report was diagnosed with CCC of the diaphragm three years after surgery, which was a shorter period of time

than those reported in previous studies. MMR deficiency following a loss of heterozygosity of a pathogenic MMR gene might act as an early event in the malignant transformation of endometriosis.

To date, few papers have reported the relationship between LS and endometrial intraepithelial neoplasia/AEH. In Lucas *et al* performed IHC analysis of 118 randomly selected endometrial intraepithelial neoplasia/AEH patients and showed loss of MMR protein expression in four patients (3.4%), two of whom were confirmed as having LS (33). Lu *et al* reported that two (3.9%) of 51 women with LS had AEH at the baseline endometrial biopsy (34). Loss of MMR protein expression in endometrial lesions has been detected in LS patients with simple EH, complicated EH, or AEH, along with MLH1 methylation (35). In a similar study, decreased MMR protein expression was observed in 7% of LS patients with normal endometrium, 40% of those with simple hyperplasia, 100% of those with complex EH without atypia, 92% of those with complex AEH, and 100% of those with EC (36). It was recently reported that elevated MSI was detected in aspirates from premalignant and malignant lesions, as well as from normal endometrium, and correlated with loss of MMR protein (37). Since loss of MSH2/MSH6 expression in AEH cells was identified in our case, IHC for MMR proteins in AEH patients may provide an opportunity to identify LS.

In conclusion, to the best of our knowledge, this is the first reported case of diaphragmatic CCC with LS. Although there are limitations such as the lack of MRI findings before surgery for the diaphragm tumor and CA125 data before the removal of the ovaries, the origin of CCC is considered to be related to malignant transformation of extrapelvic endometriosis, given the history of ovarian endometriosis. Since the diaphragmatic tumor showed MSI-high and loss of MSH2/MSH6 expression by IHC, MMR germline PVs are implicated in the malignant transformation of endometriosis. Therefore, women with endometriosis and LS are at risk of developing cancer not only in the ovaries, but also in other parts of the body, such as the abdominal cavity. In addition, our patient also had a history of AEH, which decreased the expression of MMR proteins. For AEH patients at high risk of LS based on family history, IHC screening for MMR proteins should be considered to facilitate early clinical intervention, given the possibility of EC.

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Availability of data and materials

The data presented in this manuscript are available on request from the corresponding author.

Authors' contributions

MU and TW wrote the original draft, and contributed to conception, design, data acquisition and data analysis. SS and TM contributed to data analysis, supervision, and reviewed and edited the manuscript. YK, AK, CO, TS, NK, YE and SF contributed to management of the patient and data acquisition. KF contributed to supervision, interpretation of the data and approved the final manuscript version to be published. TW and TM confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient to publish this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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