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Case report

Triple synchronous primary malignancies of the colon, endometrium and kidney in a patient with Lynch syndrome treated via minimally invasive techniques

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ABSTRACT

Coexisting primary malignancies have been described at length in the literature. While double primary malignancies are relatively common, three synchronous primary malignancies are extremely rare.

We describe a case of a 60-year-old woman undergoing surgery for a known endometrial carcinoma. The patient also had a renal mass that was identified as a clear cell renal cell carcinoma and an additional lesion in the colon that was a mucinous adenocarcinoma. Further genetic testing of the patient revealed a deleterious MSH6 mutation suggestive of Lynch syndrome. The patient had all tumors addressed by minimally invasive techniques at the same operative intervention.

It is important to consider hereditary cancer syndromes in women with a strong family history presenting with synchronous multiple primary malignancies. A multidisciplinary surgical approach is key to best practices and optimal patient outcomes.

1. Introduction

Synchronous primary tumors of the female reproductive tract are not rare conditions. Double primary malignancies have been extensively studied, with the most frequent synchronous neoplasms being endometrial and ovarian cancers. Triple primary malignancies, on the other hand, are very rare and it is necessary to distinguish the malignancies as primary versus metastases. To our knowledge, there have been few studies in the literature that demonstrate the existence of triple simultaneous neoplasms (Isin Dogan Ekici et al., 2006; Hale et al., 2011; Takatori et al., 2014; Phupong et al., 2007; Ozan et al., 2008; Capilna et al., 2014).

In this report, we identify and present the findings from a patient with synchronous endometrial carcinoma, renal cell carcinoma and mucinous adenocarcinoma with signet ring cell features of the colon. We believe this to be the first report of this histological combination of malignancies. Genetic testing of the patient was positive for a deleterious mutation in MSH6, suggestive of Lynch syndrome. A multidisciplinary surgical approach helped our patient have combined procedures done via minimally invasive approaches at one sitting with excellent surgical outcomes.

2. Case

A 60-year-old, Hispanic female gravida 3 para 3 postmenopausal female presented with symptoms of abdominal pain, bloating, flatulence, diarrhea and urinary frequency and postmenopausal bleeding. She was referred by her gynecologist after endometrial biopsy showed moderately differentiated endometrial adenocarcinoma. On preoperative PET imaging (Fig. 1) she also had a 6 cm right upper pole renal mass that was suggestive of renal cell carcinoma and a lesion in the transverse colon seen at the time of colonoscopy consistent with either a primary malignancy or metastatic disease. The patient had no significant medical or gynecologic history and a BMI of 26.3. Her family history was significant for an uncle with colon cancer (age 60), a sister with ovarian cancer (age 45), her mother had breast (age 33) and uterine cancer (age 60) and a grandmother with uterine cancer (age 50). Until now, no other family member had been tested for any hereditary cancer mutations.

After careful review of her history and risk factors, a multidisciplinary surgical approach was recommended and planned after consultation with a urologist and a colorectal surgeon. A robotic total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic and para-aortic lymph node sampling was planned in combination with a hand assisted laparoscopic right nephrectomy and right transverse colectomy with a stapled ileocolic side to side functional end to end anastomosis as per the surgeons' preferences. The nephrectomy was performed first followed by the colectomy using the same hand

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assisted access. The hand assisted incision was closed and at its superior margin a robotic trocar was inserted, the patient repositioned and draped and the robotic gynecologic procedure performed last (Fig. 3). Total operative time was 402 min from first skin incision to final closure. EBL was 200 cm^3 total. The patient did well and was discharged on postoperative day number 3 with no complications.

Gross specimens included right kidney, right and proximal transverse colon, uterus, cervix, bilateral fallopian tubes and ovaries, right and left periaortic lymph nodes and right and left pelvic lymph nodes (8 total nodes sampled). A 6 × 6 cm well-circumscribed encapsulated mass was found in the upper pole of the kidney and was found to be clear cell renal cell carcinoma, Fuhrman nuclear grade 2, limited to the kidney (Fig. 2). The AJCC tumor stage is T1bNxMx. The right and proximal transverse colon consisted of cecum, ascending and proximal transverse colon. There was a 2.0 × 1.5 cm mass that was found to be an infiltrating poorly differentiated mucinous adenocarcinoma with signet ring cell features involving the transverse colon and invading into the muscularis propria (Fig. 1). There was metastasis found in 1 of 26 lymph nodes, giving a final AJCC tumor stage of T2N1aMx. In the uterine fundus, there was a mass that was 1.5 × 1.0 cm. It was an endometrial adenocarcinoma, endometrioid type, FIGO grade 1 of 3, STAGE IB. The depth of invasion was 70% of the myometrium, invading 0.7 cm out of 1.0 cm. There was no tumor found within the right and left periaortic and pelvic lymph nodes sampled or in the adnexae (Fig. 1).

K-ras mutation analysis was performed on the colon adenocarcinoma, but was found to be negative. The patient elected to have genetic testing involving the following genes: EPCAM, MLH1, MSH2, MSH6, MYH and PMS2 (Myriad, Salt Lake City, UT). Analysis was done by microarray comparative genomic hybridization (microarray CGH), which revealed a 3311delTT deleterious germline mutation in the MSH6 mismatch repair gene. The patient did receive postoperative radiation for her uterine risk factors and systemic chemotherapy for her colon stage. Currently the patient is alive and free of recurrence at 24 months. Further genetic testing of family members is necessary along with immunohistochemical staining to identify subsequent decreased or absent protein expression in the MSH6 gene.

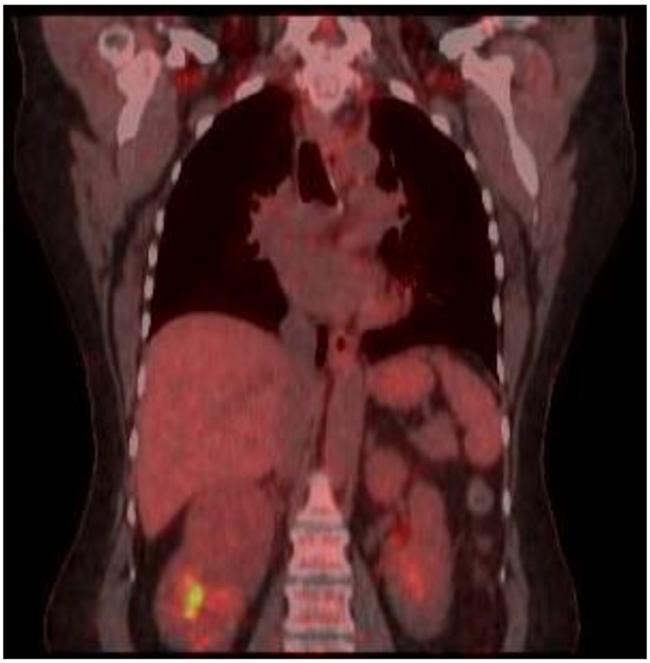

Fig. 1. Preoperative PET/CT scan showing the renal lesion.

3. Discussion

Hereditary nonpolyposis colorectal cancer (HNPCC), also referred to as Lynch syndrome, is an autosomal dominant familial cancer syndrome that arises due to mutations in DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6 and PMS2. The most commonly affected genes are MLH1 and MSH2, accounting for a total of 70–80% of cases of Lynch syndrome (Hampel et al., 2005; Baglietto et al., 2010). MSH6 mutations are less frequently encountered, accounting for about 10–20% of Lynch syndrome cancers. Women diagnosed with Lynch syndrome are predisposed to synchronous gynecologic malignancies. That being said, among women with synchronous tumors, only small percentages are found to have a diagnosis of Lynch syndrome (Kim et al., 2011; Soliman et al., 2005). Following colorectal cancer, the most common primary tumor found in women with HNPCC is endometrial cancer. Other than colorectal and endometrial cancers, patients with mismatch repair gene mutations are at risk for various other malignancies including renal, gastric, ovarian and urinary bladder cancers (Win et al., 2012). In Lynch syndrome, colorectal carcinoma is often diagnosed at a younger age (mean 45 years) compared to sporadic colorectal carcinoma in patients without Lynch syndrome (65 years) (Lynch et al., 2008). There are also certain risk factors for developing multiple malignancies (colorectal and ovarian) in women found to have endometrial cancer. This includes young age, a strong family history and cancer located in the lower uterine segment. In these cases, it is important to implement stringent preventive strategies and more effective screening methods to identify patients with multiple malignancies (Uccella et al., 2011).

The patient in this case report was diagnosed with endometrial cancer via endometrial biopsy, but it is unknown when the colorectal cancer first developed. In a study performed by Lu et al. (2005), gynecologic cancer was found to be the "sentinel cancer" and developed prior to a diagnosis of colon cancer. This is important because gynecologists treating women who are found to have endometrial cancer and a strong family history of cancer should be highly suspicious of a familial cancer syndrome and refer patients for cancer screening and genetic counseling to try and reduce morbidity and mortality. To date, no other family members have received genetic testing while this patient tested positive for an MSH6 mutation. This patient was also found to have clear cell renal carcinoma and mucinous adenocarcinoma of the colon with signet ring features. In Lynch syndrome, colorectal cancer is often found to be poorly differentiated and show signet ring cell features (Lynch et al., 2008), consistent with the findings in our patient. It is important to be aware of the cardinal features of HNPCC so that clinicians can properly identify individuals who would benefit from genetic testing. In our patient a 3311delTT deleterious germline mutation was detected. This specific germline mutation causes early truncation of the MSH6 protein at position 1106 in the amino acid sequence.

A study analyzing the risk of cancers in patients with an MSH6 mutation found that one in ten women will develop colorectal cancer by age 70, and three in ten women will develop endometrial cancer by age 70. This further translated into an 8-fold increase in the risk of colorectal cancer and a 26-fold increase in the risk of endometrial cancer compared to the general population (Baglietto et al., 2010). Another study found that the risk of colorectal cancer was 30% and the risk of endometrial cancer was 71% in women with HNPCC by age 70. Patients with MSH6 gene deletions are also found to have cancers diagnosed at later ages compared to patients with MLH1 and MSH2 gene mutations (Hendricks et al., 2004). This may alter screening guidelines in women with MSH6 mutations because cancers do not arise until later in life. Regardless, it is important that clinicians keep their suspicions high when encountering patients with synchronous primary malignancies at multiple potential sites with a coexisting strong family history. Unfortunately, it is unclear at this time if having 3 separate primaries will affect the long term prognosis of the individual tumor types when considered as if a solely occurring neoplasm. Equally important is being able to offer these patients a multidisciplinary approach to surgery. Although there

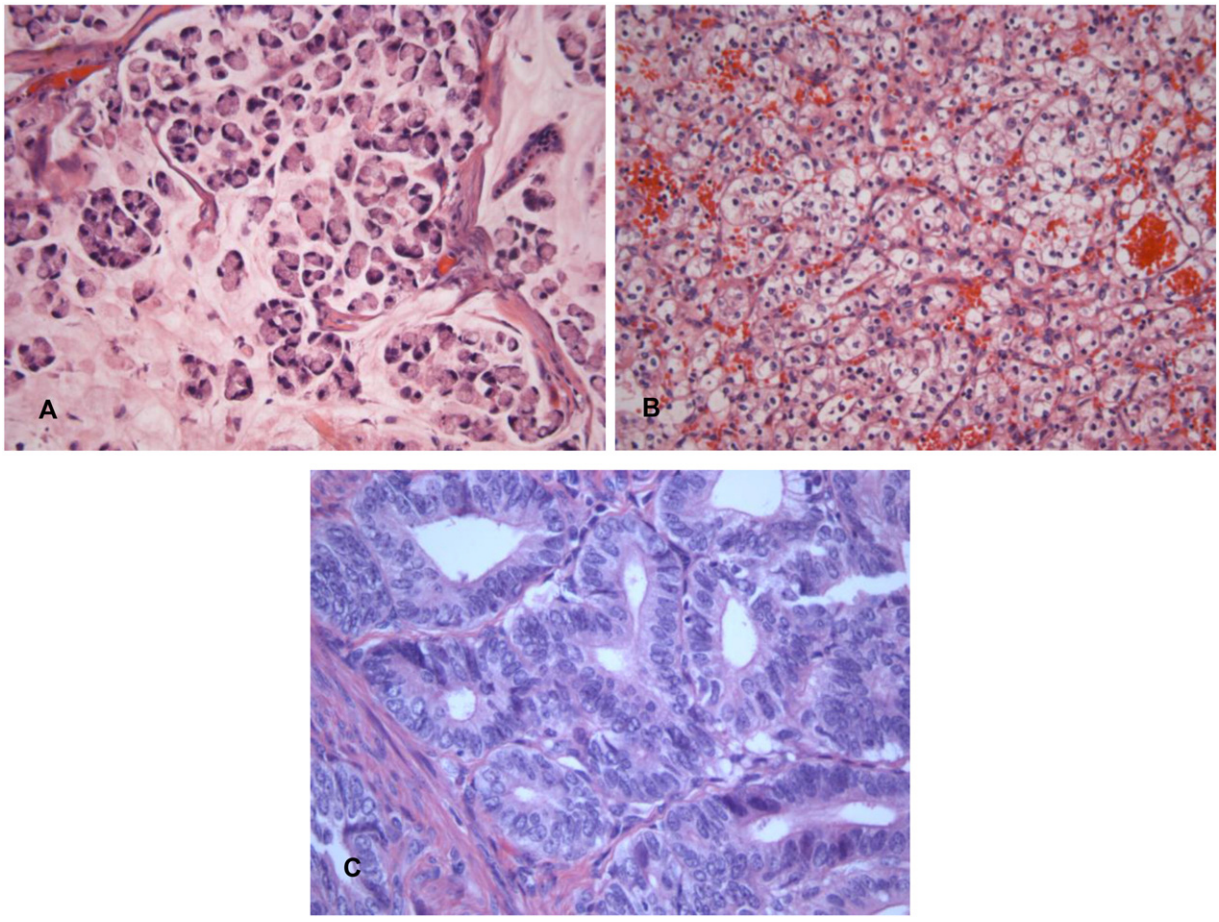

Fig. 2. A. Colon carcinoma, B. Renal cell carcinoma, C. Endometrial carcinoma.

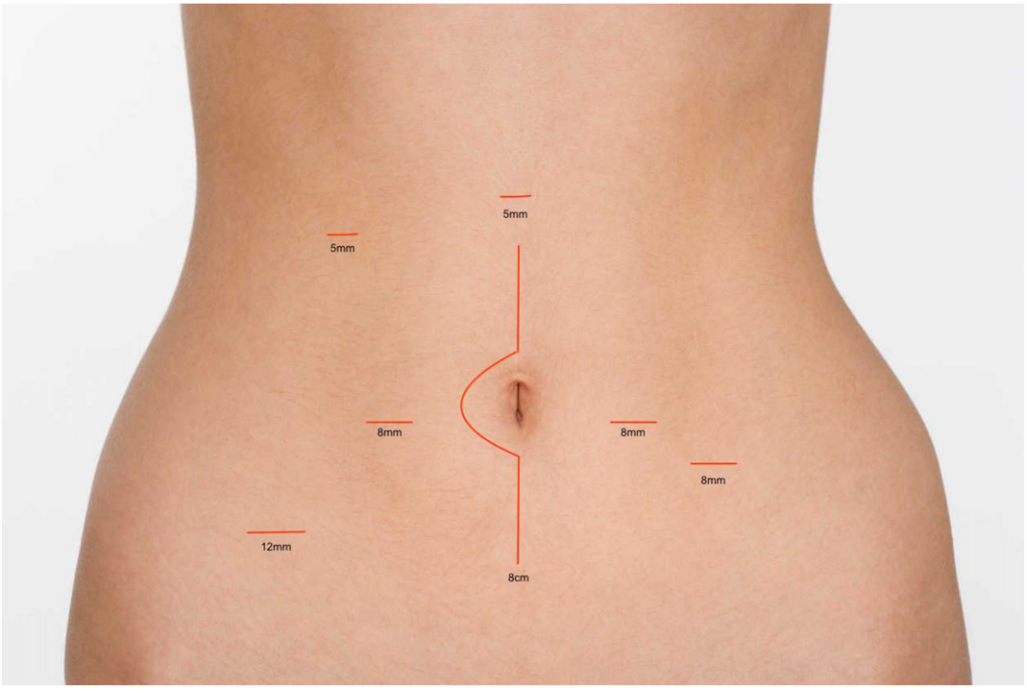

Fig. 3. Port placement.

will be increased operative times and potential morbidity related to the extensive nature of the combined surgical approach, it appears that multiple concurrent procedures can be performed safely with varying minimally invasive approaches. In this patient, the approach optimized outcomes and improved her quality of life and post-surgical recovery.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

Baglietto, L., Lindor, N.M., Dowty, J.G., et al., 2010. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J. Natl. Cancer Inst. 102, 193–201.

Capilna, M.E., Rusu, S.C., Szabo, B., Marian, C., 2014. Three synchronous primary pelvic cancers — a case report. Rev. Med. Chir. Soc. Med. Nat. Iasi 118 (1), 107–110 (Jan–March).

Hale, C.S., Lee, L., Mittal, K., 2011. Triple synchronous primary gynecologic carcinomas: a case report and review of the literature. Int. J. Surg. Pathol. 19 (4), 552–555 (August).

Hampel, H., Frankel, W.L., Martin, E., et al., 2005. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N. Engl. J. Med. 352 (18), 1851–1860.

Hendricks, Y.M.C., Wagner, A., Morreau, H., et al., 2004. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology 127, 17–25.

Isin Dogan Ekici, A., Kucukali, T., Coskun Salman, M., et al., 2006. Triple simultaneous primary gynecological malignancies in a 56-year-old patient. Int. J. Gynecol. Cancer 16 (5), 1947–1950 September.

Kim, M.K., Song, S.Y., Do, I.G., et al., 2011. Synchronous gynecologic malignancy and preliminary results of Lynch syndrome. Gynecol. Oncol. 22 (4), 233–238.

Lu, K.H., Dinh, M., Kohlmann, W., et al., 2005. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet. Gynecol. 105 (3), 569–574.

Lynch, H.T., Lynch, J.F., Lynch, P.M., et al., 2008. Hereditary colorectal cancer syndromes: molecular genetics, genetic counseling, diagnosis and management. Familial Cancer 7, 27–39.

Ozan, H., Ozerkan, K., Aker, S., Bulbul, M., 2008. A case with three primary tumors of the ovary, endometrium and gallbladder. Eur. J. Gynaecol. Oncol. 29 (5), 551–553.

Phupong, V., Khemapech, N., Triratanachat, S., 2007. Triple synchronous primary cervical, endometrial and ovarian cancer with four different histologic patterns. Arch. Gynecol. Obstet. 276 (6), 655–658 (December).

Soliman, P.T., Broaddus, R.R., Schmeler, K.M., et al., 2005. Women with synchronous primary cancers of the endometrium and ovary: do they have Lynch syndrome? J. Clin. Oncol. 23 (36), 9344–9350 (December 20).

Takatori, E., Shoji, T., Miura, Y., Takeuchi, S., Uesugi, N., Sugiyama, T., 2014. Triple simultaneous primary invasive gynecological malignancies: a case report. J. Obstet. Gynaecol. Res. 40 (2), 627–631 (February).

Uccella, S., Cha, S.S., Melton, L.J., et al., 2011. Risk factors for developing multiple malignancies in endometrial cancer patients. Int. J. Gynecol. Cancer 21 (5), 896–901 (July).

Win, A.K., Lindor, N.M., Young, J.P., et al., 2012. Risks of primary extracolonic cancers following colorectal cancer in Lynch syndrome. J. Natl. Cancer Inst. 104, 1363–1372.