



Case report

A case of ovarian endometrioid adenocarcinoma with yolk sac differentiation and Lynch syndrome



Janhvi Sookram^{a,*}, Brooke Levin^b, Julieta Barroeta^c, Kathy Kenley^d, Pallav Mehta^b, Lauren S. Krill^a

^a Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, MD Anderson Cancer Center at Cooper, Cooper University Health System, Camden, NJ, USA

^b Division of Hematology/Medical Oncology, MD Anderson Cancer Center at Cooper, Cooper University Health System, Camden, NJ, USA

^c Department of Pathology, Cooper University Health System, Camden, NJ, USA

^d Cooper University Health System, Camden, NJ, USA

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ABSTRACT

Ovarian endometrioid adenocarcinoma with yolk sac component has been reported in fewer than twenty cases in the literature. A majority of the diagnoses are described in postmenopausal women without specific reference to germline genetic testing. We describe, to our knowledge, the first case in the English literature of a premenopausal woman that presented with an ovarian endometrioid adenocarcinoma with focal yolk sac component and was subsequently found to have a germline *MSH2* mutation confirming a diagnosis of Lynch syndrome. Concurrent diagnosis of ovarian endometrioid adenocarcinoma with yolk sac tumor and Lynch syndrome is an extremely rare finding in a young patient and requires careful follow-up. Genetics evaluation and testing may be reasonable for individuals with this rare or mixed tumor pathology at young age of onset and can have clinical utility in guiding future cancer treatment or surveillance.

1. Introduction

Yolk sac tumor represents approximately 20% of malignant ovarian germ cell tumors (Dallenbach et al., 2006). They commonly arise in young premenopausal women and have relatively poor prognoses compared to other germ-cell histologic subtypes, although they generally have a favorable response to chemotherapy (Nasioudis et al., 2017). Yolk sac tumors can occur alone in a pure form or mixed with other germ cell tumors, but an association between yolk sac tumor and epithelial component is extremely rare.

Ovarian endometrioid adenocarcinoma with coexisting yolk sac tumor has been reported in fewer than twenty cases in the literature. A majority of the diagnoses are described in postmenopausal women without specific reference to germline genetic testing. Ovarian endometrioid adenocarcinoma is a more common epithelial ovarian tumor associated with Lynch syndrome; however, yolk sac, mixed ovarian tumors, and other germ cell tumors have been less frequently reported (Ketabi et al., 2011; Ryan et al., 2017; Chui et al., 2014). We present the case of a premenopausal woman presenting with an ovarian endometrioid adenocarcinoma with associated yolk sac tumor who was subsequently found to have a germline *MSH2* mutation confirming a

diagnosis of Lynch syndrome.

2. Case

A 29-year-old, nulligravid, woman presented with a 4-week history of intermittent pelvic pain. Prior to office visit, patient had an ultrasonography, which showed a large heterogeneous mass with internal septations measuring 12.6 × 11.5 × 9.6 cm in the right adnexa. Her uterus appeared unremarkable and the left ovary was not enlarged. Prior to surgery, the patient's serum CA-125 was elevated at 474 U/mL (normal: < 35 U/mL) and beta-hCG (< 2 mIU/mL), inhibin B (29 pg/mL) and alpha-fetoprotein (AFP) (3.6 ng/mL) were within normal range. At laparotomy, the right ovary was encased within a multi-loculated mass containing necrotic and friable tissue. An intraoperative pathology assessment of the right salpingo-oophorectomy specimen revealed adenocarcinoma. Due to the patient's desire for future fertility, a fertility-sparing surgery with comprehensive staging procedure including pelvic washings, omentectomy, bilateral pelvic and para-aortic lymph node dissection and peritoneal biopsies were performed.

Her postoperative clinical course was uneventful. Final histopathologic examination revealed FIGO stage IC1, ovarian endometrioid

* Corresponding author at: Cooper University Hospital, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, 2 Cooper Plaza, Suite C3067, Camden, NJ 08103, USA.

E-mail address: sookram-janhvi@cooperhealth.edu (J. Sookram).

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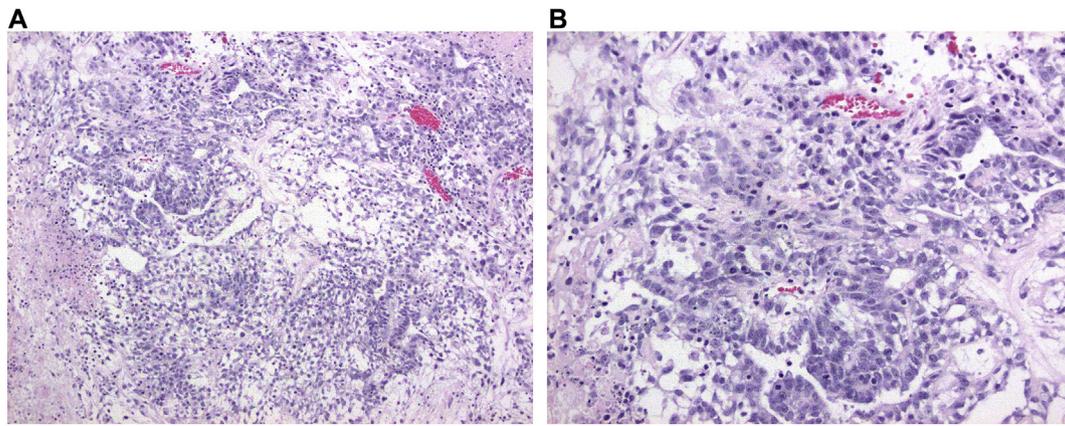


Fig. 1. A. Proliferation of endometrioid glands in a predominantly solid pattern with moderate cytologic atypia and brisk mitotic activity with associated extensive necrosis consisted with endometrioid carcinoma grade 3 (H&E 100 \times). B. Focus of yolk sac-tumor differentiation in a reticular arrangement with prominent hyaline globules represented by a black arrow (H&E 200 \times).

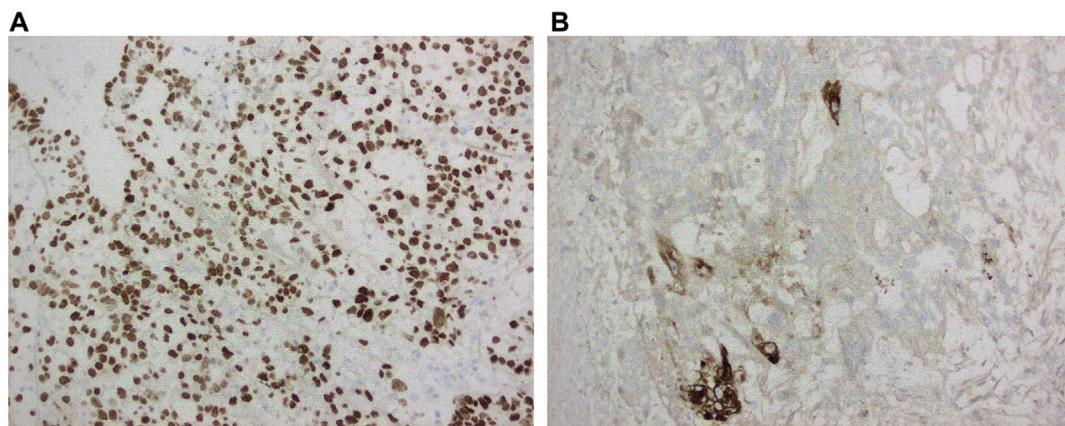


Fig. 2. Immunohistochemical staining of area morphologically compatible with yolk sac-tumor differentiation demonstrates diffuse positivity for SALL4 (A) and focal positivity for AFP (B), supporting the diagnosis (IHC 200 \times).

adenocarcinoma, grade 3, with an associated focal yolk sac tumor component. The endometrioid component demonstrated glandular morphology with cytologic atypia and brisk mitotic activity with areas of solid growth pattern with severe cytologic atypia and extensive necrosis. Immunohistochemical stains performed with adequate controls were positive for cytokeratin-7, estrogen receptor, PAX8 and patchy p16 in foci with endometrioid histology with decreased expression of CK7 and ER and overexpression of p53 within the solid areas, consistent with grade 3 endometrioid adenocarcinoma (Fig. 1). There was an additional small focus of distinctive morphology composed of epithelioid cells in a glandular and reticular arrangement with prominent hyaline globules that showed positive staining for SALL4 and AFP compatible with yolk sac tumor (Fig. 2). Although no endometriosis was identified within the fragmented ovarian tissue, focal endometriosis was present in the concurrent posterior cul-de-sac biopsy.

Additional serum tumor markers that were drawn postoperatively included lactate dehydrogenase which was noted to be elevated at 645 U/mL and inhibin A, which was normal. Moreover, given the findings of ovarian endometrioid tumor, an endometrial sampling was obtained to rule out concomitant endometrioid-type endometrial cancer that revealed benign secretory endometrium.

In the setting of grade 3 endometrioid-type histology, the patient was extensively counseled on the need for adjuvant treatment with 3–6 cycles of intravenous platinum-based therapy. The patient was also made aware that the rarity of the tumor type limited our ability to evaluate prognostication and implement optimal treatment decisions at the time. Moreover, the patient was informed that although

reproductive injury is less likely with short-term treatment, chemotherapeutic agents might slightly increase risk for ovarian insufficiency and infertility and was referred for evaluation and counseling with a reproductive endocrinologist. After adequate deliberation, the patient declined ovarian stimulation and oocyte retrieval. Her treatment plan comprised of a combination of 3 cycles of bleomycin/etoposide/cisplatin followed by 4 cycles of carboplatin/paclitaxel, which the patient completed with no significant toxicity. Serum measurements of CA-125 and lactate dehydrogenase declined to normal after two cycles of chemotherapy. Serum levels of inhibin B and AFP were also monitored periodically and remained within normal limits. A CT scan of the abdomen/pelvis with oral and intravenous contrast was performed after completion of chemotherapy that showed no evidence of disease.

The patient also completed germline genetic testing, which consisted of a 24 gene hereditary cancer panel and was diagnosed with a pathogenic mutation in *MSH2* (MutS Homolog 2), c.2038C > T (p.R680X), and a variant of uncertain significance in *ATM* (Ataxia-Telangiectasia mutated), c.9002G > A (p.S3001N). Both of the patient's birth parents were adopted and thus there was limited information regarding the health history of extended paternal and maternal biological relatives. The patient received substantial genetic counseling in this regard and was appropriately counseled about her increased risk of certain types of cancers including colorectal, endometrial and ovarian cancer. In accordance with the screening recommendations for patients with Lynch syndrome, she subsequently had a normal colonoscopy, and a negative screening bilateral

mammogram. Also, as mentioned earlier, the patient had a recent endometrial sampling, which was benign.

Eight months after completion of chemotherapy, the patient had a rise in serum CA-125 and inhibin B. Over a period of 8 weeks, serial serum levels for inhibin B were 37.4, 38.1 and 80.1 pg/mL, while that for CA-125 were 7.2, 14.6 and 10.1 U/mL. During this period, on review of systems, the patient complained of intermittent left lower quadrant pain and bloating. A CT scan of the abdomen/pelvis revealed a complex cyst measuring 6 × 3.2 cm in the left adnexa but a subsequent PET/CT imaging showed no evidence of metastatic disease or hypermetabolic activity in the adnexa. The patient was informed that based on the results of her PET/CT imaging, there was a very low suspicion for recurrent disease and the recommendation was made for surveillance with serial imaging. During her next follow-up visit, the patient decided for personal reasons that she no longer desired fertility and elected for completion surgery with total hysterectomy and left salpingo-oophorectomy. Final pathological evaluation revealed no residual malignant tumor but changes suggestive of endometriosis in the left fallopian tube and ovary. Post-surgery serum CA-125 and inhibin B levels returned to normal range.

The patient has been undergoing routine tumor surveillance and currently remains 30-months disease-free postoperatively. She has also received appropriate follow-up and screening for her newly diagnosed Lynch syndrome. Tumor markers during the patient's disease course are graphically represented in Fig. 3.

3. Discussion

Our case demonstrates an extremely rare association of ovarian endometrioid adenocarcinoma with yolk sac tumor. On our review of other reported cases, we note certain clinicopathologic characteristics that are unique to this tumor type including occurrence during perimenopausal and postmenopausal years, association with endometriosis, elevated serum AFP levels, potential for aggressive behavior, and poor response to chemotherapy. Moreover, in evaluating the patient outcomes based on prior case reports, a significant number of deaths resulted within 3–24 months of diagnosis regardless of the histologic grade of endometrioid component or stage at presentation. At present, it is unclear whether it is the endometrioid or the yolk sac tumor component that contributes to worse survival outcomes. Table 1 summarizes these tumor characteristics.

Similar to related case reports, the current case demonstrates typical immunohistochemical expression of AFP and SALL4 in the focus of yolk sac tumor with negative staining of the endometrioid component. This is in contrast to so-called endometrioid-like variants of yolk sac tumor that resemble endometrioid carcinomas that are diffusely positive for AFP and seem to occur in predominantly young women as described in

one case series (Clement et al., 1987). Given the rarity of these tumors, research regarding their histogenesis has not been performed. The hypothesis of retrodifferentiation or a neometaplastic process has been postulated to explain the lack of chemosensitivity as compared to pure germ cell tumors (Lopez et al., 2003). However, the possibility of an origin in somatic stem cells cannot be entirely excluded (Nogales et al., 1996). Despite shared histopathological findings of the current report to those described in Table 1, the relatively young age and normal serum AFP levels indicate remarkable clinical differences. Hence, it is imperative to emphasize that recognition of such rare tumor types requires a certain index of suspicion and thorough histological and immunohistochemical assessment to obtain an accurate diagnosis.

Because of the limited number of reports, there is no consensus on the optimal treatment regimen for this rare tumor type. Earlier published reports exclusively employed vincristine/dactinomycin/cyclophosphamide and cisplatin-based treatments; however, in the last two decades, bleomycin/etoposide/cisplatin has also been incorporated (Kane et al., 2004; McBee Jr. et al., 2007; Abe et al., 2008; Hong et al., 2010; Koi et al., 2014). As shown in Table 1, in an attempt to target the yolk sac and the endometrioid component, over half of the newer reports used bleomycin/etoposide/cisplatin and taxane/platinum agents. Their disease-free survival was documented up to 12–48 months depending on the years of follow-up. At this point, no conclusions can be drawn based on just a handful of reports on a reasonable and effective option for the treatment of this rare entity. Moreover, it must be emphasized that our decision to use a combination of bleomycin/etoposide/cisplatin and carboplatin/paclitaxel as an adjuvant therapy in our patient is based on the available limited evidence.

The diagnosis of Lynch syndrome is a unique aspect of this case. None of the previously published similar cases reported coexisting Lynch syndrome or related tumor/genetics testing. Testing for Lynch syndrome in ovarian cancers has recently gained attention (Chui et al., 2014; Rambau et al., 2016). Lynch syndrome is an autosomal dominant familial cancer risk syndrome that predisposes to cancers of the colon, uterus, stomach, ovary and other rare sites and is characterized by a germline mutation in one of several mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2* or *EPCAM* (Lynch and de la Chapelle, 2003). Amsterdam criteria and Bethesda guidelines were proposed to identify individuals at risk for Lynch syndrome. They included clinical criteria such as personal or family history of young onset colorectal cancer and presence of histologic features. Due to their “colon-centric schemas”, they performed poorly in identifying women with Lynch syndrome who presented with a gynecological cancer as their initial diagnosis (Lancaster et al., 2007 and Chui et al., 2013). Interestingly, one study showed that in over 50% women with Lynch syndrome, endometrial or ovarian cancer precedes development of colorectal cancer (Lu et al., 2005). Based on this, Bethesda guidelines were modified to

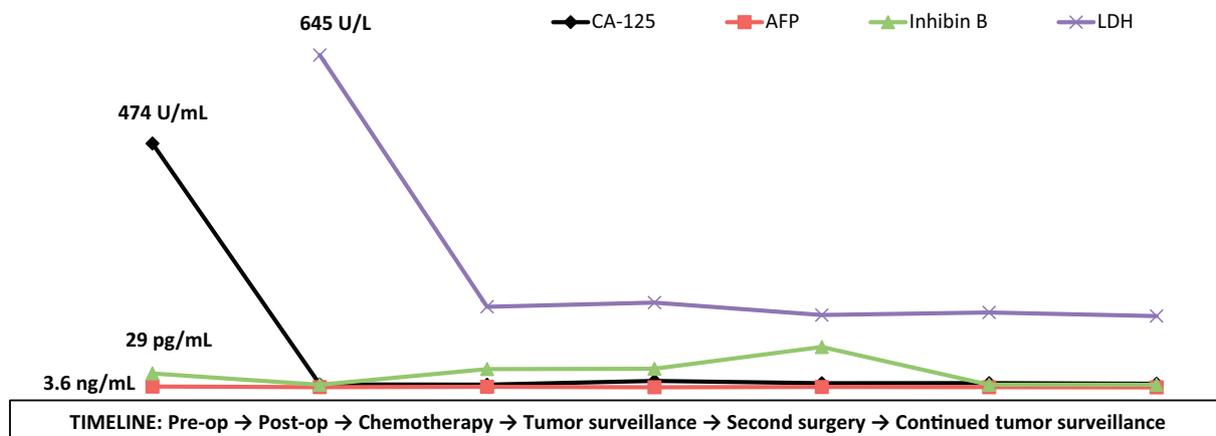


Fig. 3. Relationship between patient's disease course and tumor markers; AFP (alpha-feto protein); LDH (lactate dehydrogenase).

Table 1
Tumor characteristics of reported cases of endometrioid adenocarcinoma with yolk sac tumor.

Case	Age	Presentation	Ovarian tumor type	Stage and histologic grade	Serum AFP level (ng/mL)	Serum CA-125 (U/mL)	Surgery	Chemo-therapy	Follow-up	Endometriosis	Genetic testing
Rutgers et al. (1987)	50	Abdominal fullness palpable pelvic mass	EC-YST	IA	720	NA	TAHBSO/omentectomy	5 cycles ^a /1 cycle ^b	DOD at 8 months	Yes	NA
Nogales et al. (1996)	64	Increasing abdominal girth	EC-YST	IA/grade 2	> 300 (post-op)	Elevated	TAHBSO	3 cycles ^a	DOD at 14 months	NA	NA
	71		EC-YST	IA/grade 1	Negative 1 year after treatment	Elevated	TAHBSO	6 cycles ^c	DF at 12 months	Yes	NA
	71		EC-YST	IIIC	NA	Elevated	TAHBSO	1 cycle ^c	DOD at 8 months	NA	NA
	40		EC-YST	IV/grade 2	33	Elevated	TAHBSO	3 cycles ^c	DOD at 6 months	NA	NA
Nogales et al. (1996)	31	Acute abdomen	EC-YST/SD	IIIC/grade 1	7600 (post-op)	Elevated	RSO and second-look surgery	6 cycles ^c	DOD at 8 months	Yes	NA
Horiuchi et al. (1998)	53	High fever and lower abdominal pain, pelvic mass	EC-YST	IA/grade 1	2842.3 (pre-op)	1349 (pre-op)	TAHBSO/omentectomy/PLND	6 cycles ^d	DOD at 6 months	Yes	NA
Kamoi et al. (2002)	54	Abdominal fullness, suspected ovarian tumor	EC-YST	IC/grade 1	13,143 (pre-op)	170 (pre-op)	TAHBSO/appendectomy/omentectomy	1 cycle ^e /5 cycles ^f	DF at 21 months	Yes	NA
Kane et al. (2004)	23	Abdominal pain for 6 months	EC-YST	IIIC/grade 1	2276 (post-op)	85 (post-op)	TAHBSO/omentectomy	4 cycles ^g /2 cycles ^c	DF at 12 months	NA	NA
McBee Jr. et al. (2007)	41	Abdominal pain and large pelvic mass	EC-YST	NA	259 (post-op)	71 (pre-op)	LSO/omentectomy/PLND/PALND/resection of vaginal lesion	1 cycle ^e /3 cycles ^h	DOD at 12 months	Yes	NA
Abe et al. (2008)	52	Increasing abdominal girth and severe abdominal pain	EC-YST/SD	IC/grade 1	24, 518	8439	TAHBSO/omentectomy/PLND/PALND	3 cycles ^g /3 cycles ⁱ	DF at 20 months	No	NA
Giuliani et al. (2012)	73	Increasing abdominal girth	EC-YST	IA	Not elevated	Not elevated	BSO/omentectomy	6 cycles ^j	DF at 22 months	NA	NA
Hong et al. (2010)	35	Pelvic mass and ascites	EC-YST/SD	IIIC/grade 1	NA	137 (pre-op)	TAHBSO/omentectomy/cyoreduction	4 cycles ^g /2 cycles/ 1 cycle ^l	DOD at 12 months	Yes	NA
Koi et al. (2014)	56	Abdominal fullness, left adnexal mass	EC-YST	IIIC/grade 3	374,700 (pre-op)	88.6 (pre-op)	TAHBSO/appendectomy/omentectomy/PLND/peritonectomy	2 cycles ^g /6 cycles ^l	DF at 48 months	Yes	NA
Retamero et al. (2016)	68	Rapid abdominal distension and discomfort	EC-YST	IIIC/grade 1	Elevated	NA	TAHBSO	Unspecified number of cycles ^g	DOD 24 months	Yes	NA
Current report (2018)	29	Intermittent pelvic pain and large pelvic mass	EC-YST	IC1/grade 3	Not elevated	474 (pre-op)	RSO/omentectomy/PLND/PALND followed by TAHLSO	3 cycles ^g /4 cycles ^l	DF at 30 months	Yes	Pathogenic mutation in <i>MSH2</i> gene

Abbreviations: EC-YST, endometrioid adenocarcinoma with yolk sac tumor; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; DOD, died of disease; NA, not available; DF, disease-free; EC-YST/SD, endometrioid adenocarcinoma with yolk sac tumor and squamous differentiation; RSO, right salpingo-oophorectomy; PLND, pelvic lymphadenopathy; PALND, paraaortic lymphadenopathy; LSO, left salpingo-oophorectomy.

^a Vincristine/dactinomycin/cyclophosphamide.

^b Cisplatin/vinblastine.

^c Cisplatin-based.

^d Vinblastine/pepleomycin/cisplatin/actinomycin D/cyclophosphamide.

^e Intraperitoneal carboplatin.

^f Vinblastine/etoposide/cisplatin.

^g Bleomycin/etoposide/cisplatin.

^h Etoposide/cisplatin.

ⁱ Paclitaxel or docetaxel/carboplatin.

^j Ifosfamide/cisplatin.

include endometrial cancer as a sentinel cancer (Umar et al., 2004). At this time, however, there is a lack of definitive recommendation for ovarian cancer patients to undergo evaluation for MMR defects.

Lynch syndrome accounts for the second most common cause of inherited ovarian cancer after BRCA1/BRCA2. Lifetime risk for Lynch syndrome-associated ovarian cancer is approximately 5–24% (Lynch and de la Chapelle, 2003). Most ovarian cancers associated with germ line BRCA mutations are high-grade and advanced-stage serous carcinomas whereas those associated with Lynch syndrome typically present at a young age with most tumors being early-stage and often with endometrioid or clear cell histology (Ketabi et al., 2011; Ryan et al., 2017; Chui et al., 2014). Several studies have also noted a higher incidence of MMR protein deficiency by immunohistochemistry and microsatellite instability in endometrioid and clear cell subtype compared to high-grade serous carcinomas (Ketabi et al., 2011; Ryan et al., 2017; Chui et al., 2013; Watson et al., 2001). In the absence of precisely defined guidelines and accumulating evidence on pathologic features of Lynch syndrome-associated ovarian cancers as well as increasing use of multi-gene panel testing for hereditary cancer syndromes, it seems reasonable to perform testing for Lynch syndrome on the basis of patient's young age, tumor subtype and MMR deficiency by immunohistochemistry.

In summary, at this time, there remains limited evidence to support an ideal first-line chemotherapy regimen for this tumor type. Though a rare tumor type, ovarian endometrioid adenocarcinoma with yolk sac tumor may present in individuals with Lynch syndrome. Genetics evaluation and testing should be performed for individuals presenting with this rare or mixed tumor pathology especially at a young age of onset because these can have clinical utility in guiding future cancer treatment or surveillance. If pathogenic mutations are found, they should be reported along with treatment regimens and oncologic outcomes so a better collective understanding of this rare entity can be achieved in the future. We conclude that both clinical management of Lynch syndrome and diligent observation for recurrent disease are paramount in decreasing morbidity and mortality associated with this intriguing case.

Author contribution

Authors JS and BL made substantial contributions to the conception, literature review, data-analyses, and writing of the manuscript abstract and draft.

KK, JB, and PM participated in drafting and revising the article and contributing to the data collection and review of literature. JB and LK provided scientific suggestions and contributed to the design of the work and helped revise the final manuscript.

All authors approved the final version of the manuscript.

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