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CASE REPORT

Mixed high-grade serous and large cell neuroendocrine carcinoma arising from rectal endometriosis 11 years after hysterectomy

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Abstract

The malignant gastrointestinal endometriosis transformation is represented by endometriosis-associated intestinal tumors. Endometrioid adenocarcinoma and clear cell adenocarcinoma are most common among the endometrial cancers of all organs. Only four cases of mixed serous carcinoma and large cell neuroendocrine carcinoma have been reported, and all these cases originated from the uterus. A 59-year-old woman with a month's history of bloody stools was admitted. She was stable until the hematochezia occurred but is 11 years post-hysterectomy. A circumferential type-3 advanced upper rectum tumor was seen on colonoscopy. Adenocarcinoma was revealed from the forceps biopsies of the type-3 tumor component. Computed tomography showed narrowed lumen with a thickened rectum wall, a continuing mass, and a component on the anorectal side. Swollen lymph nodes were observed around the rectum, but no distant metastatic lymph nodes or organs were found. To treat the lesion, rectal surgical resection with D3 lymph node dissection was performed. Histological examination revealed combined high-grade serous and large cell neuroendocrine carcinomas. Tumor was contiguous to the endometrium in the sub-serosa. Endometriosis was determined to be the origin of both carcinomas. Therefore, endometriosis-associated intestinal tumors should be included in the differential diagnosis when rectal tumors with cystic structures are found post-hysterectomy.

Keywords Colonoscopy · Ectopic endometriosis · Endometriosis-associated intestine tumor · Large cell neuroendocrine carcinoma · Serous carcinoma

Introduction

Endometriosis is a disease caused by the ectopic growth of endometrial tissue outside the uterine cavity. Carcinoma-associated endometriosis is found in 0.7–1.0% of endometriosis patients and is often found in the ovaries as endometriosis has a neoplastic character. Intestinal endometriosis is reported to account for 3.8–37% of all endometriosis patients [1–4]. Endometriosis-associated intestinal tumors (EAIT) are carcinomas originating from intestinal endometriosis, which are rare [5]. Regarding the histological endometrial carcinoma subtype, large cell neuroendocrine carcinomas (LCNECs) are rare [6–20]. Moreover, mixed high-grade serous carcinoma (HGSC) and LCNEC were only reported in four cases, and all four cases had a uterine origin [8, 16, 19, 20]. No paper has reported an EAIT histologically diagnosed as HGSC or LCNEC.

Case report

A 59-year-old woman was referred to our institution with a one-month history of bloody stools and abdominal pain. She had no history of periodic abdominal pain, hematochezia, or melena, with no evidence of endometriosis. She was gravida 2, para 3. There was a history of hysterectomy for uterine fibroids at age 48. She never smoked and did not drink. Her family had no carcinoma history. The abdomen was soft and nontender with no evidence of abdominal tumor on examination. On admission, initial examinations revealed absence of anemia (hemoglobin, 12.2 g/dL; white cell count, 8500/μL;

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and platelet, 332,000/μL). Inflammatory markers (C-reactive protein, 0.28 mg/dL), liver function tests (bilirubin, 0.48 mg/dL; alkaline phosphatase, 185 IU/L; and alanine transaminase, 9 IU/L), and renal function tests (blood urea nitrogen, 14.4 mg/dL; creatinine, 0.51 mg/dL) were within normal levels. The albumin level was low (3.8 g/dL) and cancer antigen 19-9 level was elevated (84.9 U/mL). Colonoscopy (CS) was performed which showed a circumferential type-3 tumor of the upper rectum with a yellowish elevated component on the anal side (Fig. 1a, b). The endoscope was not able to pass through the narrowed part of the lesion. Barium enema X-ray showed an "apple core"—like appearance in the upper rectum (Fig. 1c). Contrast-enhanced computed tomography (CT) showed a thickened rectal wall, a 100-mm tumor with a 27-mm contrast-enhanced component on the anorectal side adjacent to the thickened wall, and a 65-mm cystic component protruding to the sacral side (Fig. 2a, b). It also showed swollen regional lymph nodes indicative of metastasis.

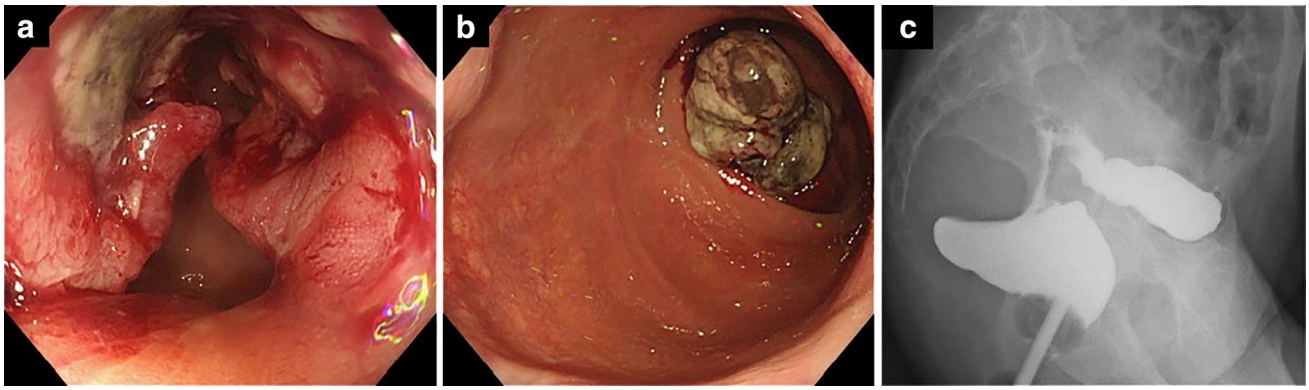

Fig. 1 Rectal lesion images. **a** Colonoscopy showed the sub-circumferential tumor with an ulcer at its center. **b** Observations from the lower rectum showed a yellow raised component on the tumor apex. **c** Barium enema revealed a rectal stenosis due to the tumor

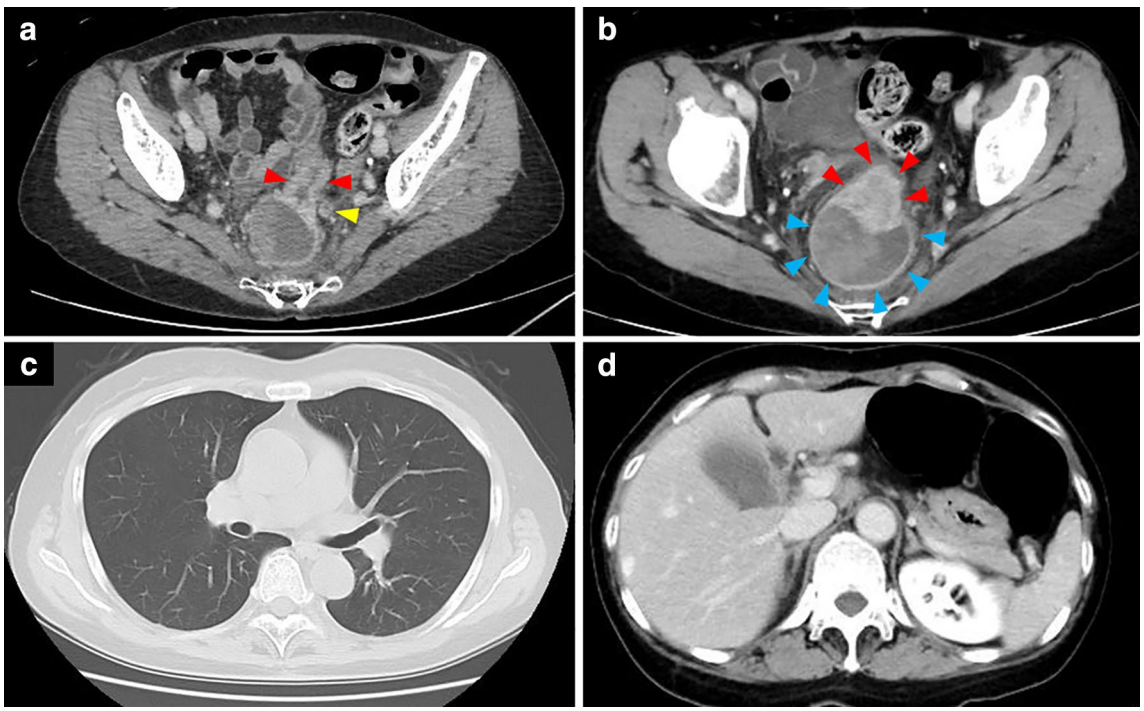

Fig. 2 Computed tomography (CT) images of the lesion in the rectum. **a** CT images of the delayed phase showed a thickening of the wall (red arrows) narrowing of the intestinal lumen and regional lymph node metastasis (yellow arrows). **b** CT images showed a 65-mm cystic component protruding from the posterior rectal wall toward the sacral side (blue arrows) and the 27-mm contrast-enhanced solid component at the posterior wall (red arrows) protruded out, pushing the cystic component on the anal side. **c**, **d** CT showed no metastases in her lung, liver or bones and no pleural effusion

However, no obvious nodules susceptible to distant metastasis or other tumors were observed (Fig. 2c, d). Histological evaluation of forceps-biopsy specimens obtained from type-3 tumor component revealed adenocarcinoma (poorly differentiated adenocarcinoma > moderately differentiated adenocarcinoma). The cystic component could not be definitively pathologically diagnosed preoperatively since it was difficult to perform fine needle aspiration. Therefore, we diagnosed the clinical stage of the colorectal adenocarcinoma was cIIIb (cT4aN1bM0) and the patient underwent rectal resection with D3 lymph node dissection. There were no nodules indicative of endometriosis during surgery on the surface of the peritoneum and mesentery.

The surgical pathological specimen revealed two carcinomas contiguous to the stroma like endometrium in the sub-serosa (Figs. 3, 4). The tubular structure cells on the oral side were positive for cytokeratin (CK) 7, cluster of differentiation (CD) 10, progesterone receptor (PgR), and paired-box gene 8 (PAX8), but negative for CK20, caudal-related homeobox transcription factor 2 (CDX2), estrogen receptor (ER), Wilms' tumor 1 (WT-1), and vimentin. The cells of the solid alveolar structure on the anal side were positive for synaptophysin, CD56, Ki-67 (80–90%) and PgR, and negative for chromogranin, CK7, CK20, CDX2, ER, CD10, WT-1, vimentin, and PAX8. Overexpression of p53 was seen in two components (Fig. 4). The cells of the structure were similar to the endometrial stroma and were positive for ER, PgR, and CD10. All structures were diagnosed to be of the same origin since the staining results of PgR and CD10 were consistent (Figs. 5, 6). The pathological findings aided in precisely diagnosing the "rectal adenocarcinoma" as mixed cell carcinoma, HGSC (80%), and LCNEC (20%) arising from rectal endometriosis. The pathological stage of the lesion was confirmed as pIIIc; 105 × 40 mm, pT4a, INFb > INFa, Ly1c, V1c (EM), Pn1b, pPM0 (70 mm), pDM0 (3 mm), pRMX, pN2b (10/13), and cM0. Endoscopic images and histopathological findings comparison revealed that the type-3 tumor component was HGSC, and the yellowish elevated component was LCNEC.

Whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography–CT revealed multiple lesions with intense FDG avidity indicative of bone and liver metastases and cancerous pleurisy two months later from the surgery. The patients received chemotherapy with carboplatin and etoposide, followed by FOLFOX with bevacizumab. However, both therapies resulted in progressive disease. Her general condition deteriorated and she died six months after diagnosis.

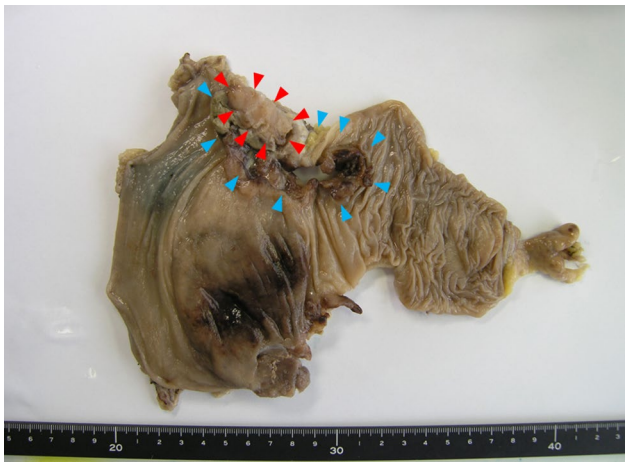

Fig. 3 Surgically resected specimen. Type-1 component (red arrows) and type-3 component with perforation of the intestinal wall (blue arrows) was found. Serous fluid was observed from perforation in the cystic component at the time of surgery

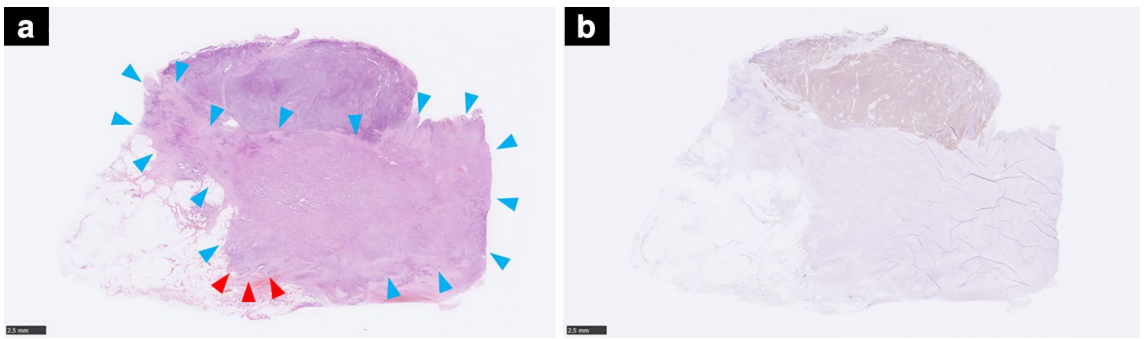

Fig. 4 Hematoxylin and eosin stain in the surgical resected specimen. **a** Hematoxylin and eosin stain showed two components; one component (blue arrows) was contiguous to the stroma like endometrium (red arrows) in the sub-serosa. The cancer cells above the component proliferated to the surface layer. There was a slight necrotic layer on the surface and no coverage of non-neoplastic colorectal mucosa. **b** Above component was positive for cluster of differentiation (CD) 56. Above component was partly mixed and contiguous to one component. CD 56 positive component was consistent with a yellowish elevated component observed on endoscopy

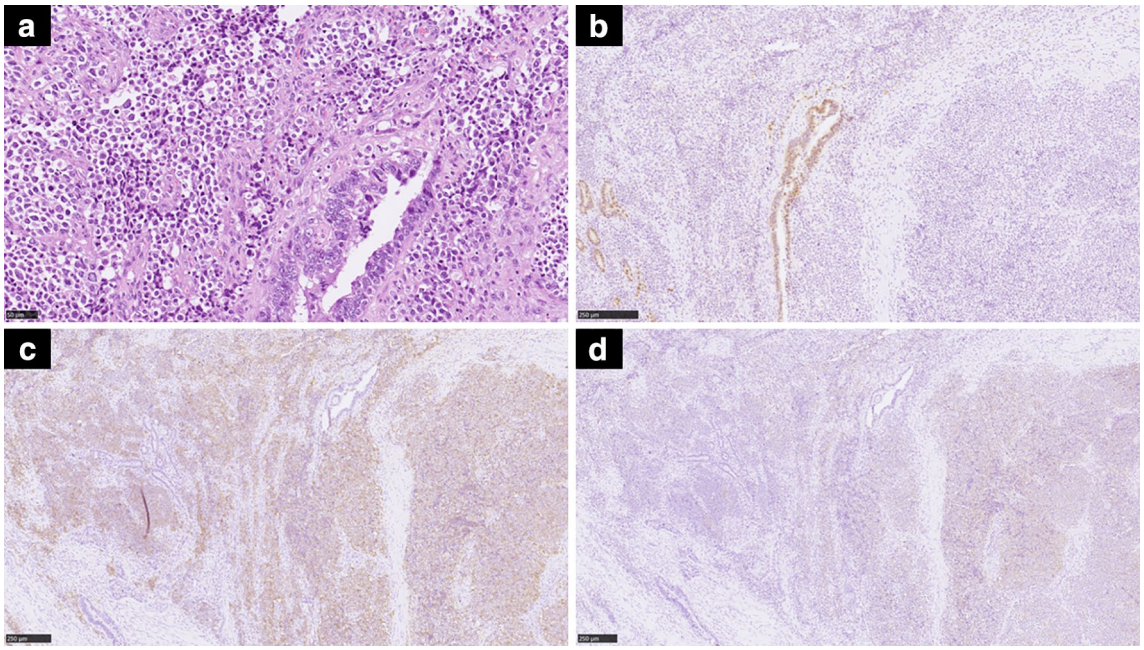

Fig. 5 High-magnified histological features of the mixed high-grade serous carcinoma (HGSC) and large cell neuroendocrine carcinoma (LCNEC). **a** Hematoxylin and eosin stain showed HGSC that typical epithelium with distorted, swollen and densely stained nucleus was invasively proliferating with tubular of the fused glands. LCNEC was solid alveolar legion with poor cell connectivity and the N/C ratio were highly elevated. **b** There cancer cells were positive for paired-box gene 8 in HGSC. **c** There cancer cells were positive for cluster of differentiation 56 in LCNEC. **d** The cancer cells were positive for synaptophysin in LCNEC

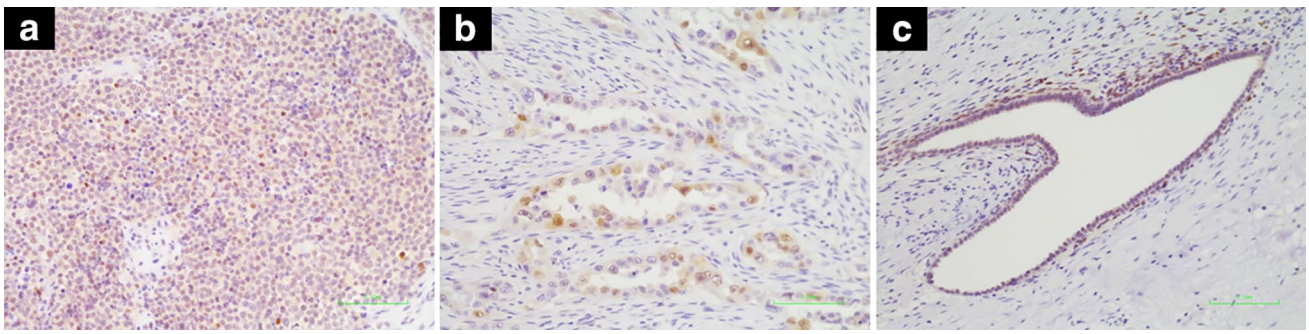

Fig. 6 Histological findings with immunostaining for progesterone receptor (PgR). **a** The cancer cells were positive for PgR in large cell neuroendocrine carcinoma. **b** The cancer cells were positive for PgR in high-grade serous carcinoma. **c** The cells of the endometrial grands and stroma were positive for PgR

Discussion

In this case, mixed HGSC and LCNEC as EAIT was diagnosed in the surgical specimen. This is the first report of such a case in our estimation.

The differentiation between EAIT and typically colorectal adenocarcinoma is the first significant point of this paper. About 70% of patients with EAIT are women in their late 30s to early 50s. The most common signs and symptoms of EAIT are abdominal or pelvic pain, bloody stools, and pelvic or abdominal mass [21]. The site of origin of EAIT is reported to be 77% in the rectum and sigmoid colon [1, 21]. The cystic lesion located in the outer bowel wall on CT was the point of differential diagnosis of colonic carcinoma in this case. Pelvic cystic lesions are known to occur in epithelial ovarian tumors, such as serous carcinomas, mature cystic teratomas, metastatic tumors, and lymphangiomas. On the other hand, typical colorectal carcinoma rarely shows cystic lesions. We first considered the lesion to be a carcinoma of rectal origin since the histological evaluation of the forceps biopsies revealed adenocarcinoma. We retrospectively reviewed the biopsy specimen, but it was difficult to be differentially

diagnosed by hematoxylin and eosin stain in the biopsy specimen since poorly differentiated adenocarcinoma and neuroendocrine carcinoma were similar in structure. Typically, patients with EAIT have undergone one or more surgical procedures aimed at treating the endometriosis, often culminating in a total hysterectomy and bilateral salpingo-oophorectomy [21]. EAIT is one of the differential diagnoses when a patient with a history of gynecologic surgery develops atypical colorectal carcinoma.

The finding of LCNEC as EAIT is the second significant point of this paper. LCNEC is a rare histological type of endometrial carcinoma and accounts for 1% of all the endometrial carcinomas [22]. Serous carcinoma is consistent with endometrial origin, but LCNEC is not. LCNEC usually does not meet the EAIT criteria. Sampson formulated criteria used for identifying EAIT [23]. These are: (1) the neoplasms have Mullerian characteristics; they resemble tumors typically associated with an endometrial origin; (2) the tumors are contiguous to or admixed with foci of endometriosis located in the bowel; and (3) the tumors do not represent obvious metastases from gonadal or extra-gonadal neoplasms. In the present case, the staining results of PgR and CD10 were consistent in all three components. Hence, all structures were diagnosed to be of the same origin. We speculated that serous carcinoma arose from intestinal endometriosis because of each element's location, and then a portion of it changed to LCNEC and proliferated. We finally diagnosed EAIT as our case met these criteria. Whether conversion of a serous carcinoma to a LCNEC is possible remains controversial. Direct invasion from other organs was unlikely because the uterus had been removed and the ovaries were anatomically distant from the rectum. In a paper on a case of LCNEC with concomitant endometriosis, it was reported that LCNEC components developed according to stepwise endometrioid carcinoma tumorigenesis, including phosphatase and tensin homolog inactivation [24]. The paper also reported that a CTNNB1 mutation is possible and that the independent CTNNB1 mutation determined the fate of the precursor lesion. Further analyses are required to confirm our speculation.

Endometrial LCNEC appears to have an aggressive course with a strong propensity for distant metastasis and rapid recurrence [17] even for early stages. Three of the patients were in the early stages at the time of diagnosis, with documented recurrence/persistence and metastases [6, 10, 15]. In addition, it has been reported that most of the patients with disseminated EAIT died within 2 years, with a 5-year survival rate of only 12.5% [25]. In four reported cases of combined HGSC and LCNEC, the overall survivals have not been reported. Endometrial LCNEC is often treated like standard endometrial adenocarcinoma with primary surgical resection, and adjuvant radiation and chemotherapy. There were four patients who were reported to have received primary surgical resection and chemotherapy; two cases received platinum-based therapy, and three cases received radiation therapy. In our case, complete removal was accomplished through surgery. However, due to the advanced stage, the cancer recurred quickly, as previously reported. She received chemotherapy, including platinum, but did not adequately control carcinoma growth. She was unable to receive radiation therapy because metastases have appeared. Very little is known regarding optimal treatment and response as HGSC and LCNEC of the endometrium is rare carcinoma, especially in the case of multiple metastases.

In conclusion, this is our first case of mixed HGSC and LCNEC as EAIT and it appeared to have an aggressive course. It needs to be differentiated from EAIT when atypical colorectal carcinomas are found, because it requires multidisciplinary treatment.

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Author contributions Conceptualization, TY and TH. Methodology, TY, TH, and YW. Formal Analysis, TY Investigation, TY, YW, HS, YT, NA, CH, and HK. Resources, TY, TH, and YW Writing–Original Draft Preparation, TY and TH Writing–Review and Editing, YW and MK. Supervision, HO. All authors have read and approved the final manuscript.

Declarations

Conflict of interest Takumi Yanagita, Takuto Hikichi, Yuichi Waragai, Hiroshi Shimizu, Yuta Takahashi, Naoto Abe, Choichiro Hashimoto, Hiromi Kumakawa, Masao Kobayakawa, Hiromasa Ohira declare that they have no conflict of interest.

Human and animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from this patient for being included in the paper.

References

1. Yantiss RK, Clement PB, Young RH. Endometriosis of the intestinal tract: a study of 44 cases of a disease that may cause diverse challenges in clinical and pathologic evaluation. Am J Surg Pathol. 2001;25:445–54.
2. Macafee CH, Greer HL. Intestinal endometriosis. A report of 29 cases and a survey of the literature. J Obstet Gynaecol Br Emp. 1960;67:539–55.
3. Orbuch IK, Reich H, Orbuch M, et al. Laparoscopic treatment of recurrent small bowel obstruction secondary to ileal endometriosis. J Minim Invasive Gynecol. 2007;14:113–5.
4. Paksoy M, Karabiçak I, Ayan F, et al. Intestinal obstruction due to rectal endometriosis. Mt Sinai J Med. 2005;72:405–8.

5. Heaps JM, Nieberg RK, Berek JS. Malignant neoplasms arising in endometriosis. Obstet Gynecol. 1990;75:1023–8.
6. Mulvany NJ, Allen DG. Combined large cell neuroendocrine and endometrioid carcinoma of the endometrium. Int J Gynecol Pathol. 2008;27:49–57.
7. Albores-Saavedra J, Martinez-Benitez B, Luevano E. Small cell carcinomas and large cell neuroendocrine carcinomas of the endometrium and cervix: polypoid tumors and those arising in polyps may have a favorable prognosis. Int J Gynecol Pathol. 2008;27:333–9.
8. Posligua L, Malpica A, Liu J, et al. Combined large cell neuroendocrine carcinoma and papillary serous carcinoma of the endometrium with pagetoid spread. Arch Pathol Lab Med. 2008;132:1821–4.
9. Terada T. Large cell neuroendocrine carcinoma with sarcomatous changes of the endometrium: a case report with immunohistochemical studies and molecular genetic study of KIT and PDGFRA. Pathol Res Pract. 2010;206:420–5.
10. Deodhar KK, Kerkar RA, Suryawanshi P, et al. Large cell neuroendocrine carcinoma of the endometrium: an extremely uncommon diagnosis, but worth the efforts. J Cancer Res Ther. 2011;7:211–3.
11. Shahabi S, Pellicciotta I, Hou J, et al. Clinical utility of chromogranin A and octreotide in large cell neuro endocrine carcinoma of the uterine corpus. Rare Tumors. 2011;3: e41.
12. Makihara N, Maeda T, Nishimura M, et al. Large cell neuroendocrine carcinoma originating from the uterine endometrium: a report on magnetic resonance features of 2 cases with very rare and aggressive tumor. Rare Tumors. 2012;4: e37.
13. Rivera G, Niu S, Chen H, et al. Collision tumor of endometrial large cell neuroendocrine carcinoma and low-grade endometrial stromal sarcoma: a case report and review of the literature. Int J Surg Pathol. 2020;28:569–73.
14. Nguyen ML, Han L, Minors AM, et al. Rare large cell neuroendocrine tumor of the endometrium: a case report and review of the literature. Int J Surg Case Rep. 2013;4:651–5.
15. Erhan Y, Dikmen Y, Yucebilgin MS, et al. Large cell neuroendocrine carcinoma of the uterine corpus metastatic to brain and lung: case report and review of the literature. Eur J Gynaecol Oncol. 2004;25:109–12.
16. Pocrnich CE, Ramalingam P, Euscher ED, et al. Neuroendocrine carcinoma of the endometrium: a clinicopathologic study of 25 cases. Am J Surg Pathol. 2016;40:577–86.
17. Tu YA, Chen YL, Lin MC, et al. Large cell neuroendocrine carcinoma of the endometrium: a case report and literature review. Taiwan J Obstet Gynecol. 2018;57:144–9.
18. Jenny C, Kimball K, Kilgore L, et al. Large cell neuroendocrine carcinoma of the endometrium: a report and review of the literature. Gynecol Oncol Rep. 2019;28:96–100.
19. Hu R, Jiang J, Song G, et al. Mixed large and small cell neuroendocrine carcinoma of the endometrium with serous carcinoma: a case report and literature review. Medicine. 2019;98: e16433.
20. Hardy LE, Chaudry Z, Wan K, et al. Primary mixed large cell neuroendocrine and high grade serous carcinoma of the endometrium. BMJ Case Rep. 2020;13: e234977.
21. Slavin RE, Krum R, Van Dinh T. Endometriosis-associated intestinal tumors: a clinical and pathological study of 6 cases with a review of the literature. Hum Pathol. 2000;31:456–63.
22. Howitt BE, Kelly P, McCluggage WG. Pathology of neuroendocrine tumours of the female genital tract. Curr Oncol Rep. 2017. https://doi.org/10.1007/s11912-017-0617-2.
23. Sampson JA. Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. Arch Surg. 1925;10:1–72.
24. Ariura M, Kasajima R, Miyagi Y, et al. Combined large cell neuroendocrine carcinoma and endometrioid carcinoma of the endometrium: a shared gene mutation signature between the two histological components. Int Cancer Conf J. 2017;6:11–5.
25. Abu MA, Sinha P, Totoe L, et al. Endometrial cancer thirteen years after total abdominal hysterectomy and bilateral salpingo-oophorectomy and hormone replacement therapy: a case report. Eur J Gynaecol Oncol. 1997;18:482–3.