Gynecologic Oncology Reports 58 (2025) 101721

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Triple synchronous primary cancers comprising large cell neuroendocrine carcinoma of the lower uterine segment and endometrioid carcinomas of the uterine corpus and the right ovary-a rare combination: A case report

Kaichiro Yamamoto [a,*], Shin-ichi Nakatsuka [b], Tomochika Goto [c], Reiko Samoto [a], Aki Minami [a], Masatoshi Imamura [a]

[a] Department of Obstetrics and Gynecology, Ikoma City Hospital, Ikoma, Nara, Japan
[b] Department of Pathology, Yao Tokushukai General Hospital, Yao, Osaka, Japan
[c] Department of Internal Medicine, Ikoma City Hospital, Ikoma, Nara, Japan

ARTICLE INFO

Keywords:
Synchronous cancer
Triple primary cancer
Neuroendocrine carcinoma
Lower uterine segment
Endometrioid endometrial carcinoma
Endometrioid ovarian carcinoma

ABSTRACT

We report a rare case of triple primary cancers in a 52-year-old woman who presented with abdominal pain and fever. Diagnostic imaging and subsequent histopathological evaluation revealed independent primary endometrioid carcinomas of the ovary and uterine corpus proper (UC), as well as large cell neuroendocrine carcinoma (LCNEC) originating from the lower uterine segment (LUS). Surgical resection was performed, followed by adjuvant chemotherapy (irinotecan and cisplatin). The patient demonstrated no recurrence at the 10-month follow-up.

This case highlights the importance of accurate pathological differentiation, as prognosis and treatment depend on distinguishing independent primary tumors from metastatic lesions. This rare case of triple synchronous malignancies emphasizes the need for a multidisciplinary approach to ensure precise diagnosis and optimal management. Comprehensive molecular studies and advanced imaging techniques may further improve outcomes in such complex cases.

1. Introduction

Triple primary malignancies involving synchronous endometrioid carcinomas of the ovary and UC, along with LCNEC of the LUS, are exceedingly rare. Such cases provide unique insights into the mechanisms of tumor development and progression, as well as significant challenges in clinical diagnosis and management.

Endometrioid carcinoma, the most common histological type of endometrial and ovarian cancer, frequently arise in association with predisposing conditions such as endometriosis (Pearce et al., 2021). In contrast, LCNEC is a highly aggressive and rare neoplasm typically found in the uterine cervix or corpus, characterized by neuroendocrine differentiation and rapid progression (Kobayashi et al., 2017). The synchronous occurrence of these histologically distinct malignancies raises intriguing questions about shared genetic pathways, potential precursor lesions, and the impact of the tumor microenvironment.

This report explores a unique case of triple primary malignancies, focusing on the clinical presentation, histopathological findings, and molecular features. Understanding such rare presentations can provide valuable insights for personalized oncology care and highlight areas for future research.

2. Case presentation

A 52-year-old woman presented to our hospital (Ikoma city hospital) with abdominal pain and fever for 4 days. Blood tests showed CRP at 12.96 mg/dl and WBC at 28,000/μl. She had a fever of 38.3 °C and was urgently admitted to the internal medicine department. Initially, Cefmetazole Sodium was administered intravenously for presumed pelvic inflammatory disease, which resulted in improvement. She was referred to the gynecology department as that concurrent pelvic magnetic resonance imaging (MRI) showed solid lesions of the right ovary and possibly LUS (Fig. 1A, B). Transvaginal ultrasound revealed endometrial and the right ovarian tumor. Concurrent endometrial biopsy indicated cancer with focal neuroendocrine differentiation. Serum carbohydrate antigen (CA)-125 was elevated to 296.2 U/mL (normal range 0–28 U/

* Corresponding author.
E-mail address: yamamotokaichiro@gmail.com (K. Yamamoto).

https://doi.org/10.1016/j.gore.2025.101721
Received 11 January 2025; Received in revised form 5 March 2025; Accepted 14 March 2025
Available online 16 March 2025

mL), and carcinoembryonic antigen (CEA), neuron specific enolase (NSE), CA-199 were normal. She underwent radical hysterectomy, bilateral salpingo-oophorectomy and bilateral pelvic lymph node dissection for the diagnosis of endometrial carcinoma and ovarian carcinoma. The *para*-aortic lymph node dissection was not performed due to excessive bleeding.

The pathological diagnosis revealed LCNEC of the LUS (Fig. 1C, 2A), endometrioid carcinoma (Grade 1) of the UC and endometrioid carcinoma (Grade 2) of the right ovary. The LCNEC showed positive staining for neuroendocrine markers chromogranin, synaptophysin, and CD56 on immunohistochemistry (Fig. 2B, C and D). The cancer was primarily located in the LUS and had spread to the cervix, showing stromal invasion. There was significant lymphovascular invasion. The surgical margins were negative. The endometrioid carcinoma of the UC was considered to arise from the uterus due to the presence of atypical endometrial hyperplasia in the surrounding flat endometrium (Fig. 3A). The cancer infiltration was confined to less than half of the myometrium in the uterine body, and the surgical margins were negative. The endometrioid carcinoma of the right ovary was considered to be of ovarian origin, given the coexistence of borderline endometrioid tumors and endometriotic cysts (Fig. 3B). The peritoneal washing sample was negative. A total of 20 lymph nodes were evaluated and all were reported as negative. The microsatellite instability (MSI) analysis for tumors was negative.

Final pathology result was reported as synchronous stage II LCNEC of the LUS, stage IA grade 1 endometrioid carcinoma of the UC and stage IC1 (capsular rupture caused by surgical manipulation) grade 2 endometrioid carcinoma of the right ovary. All of the three tumors were accepted as different primaries due to final pathologic evaluation. Postoperative 6 courses of chemotherapy with irinotecan and cisplatin have been completed. At ten months postoperatively, no signs of recurrence have been observed.

3. Discussion

Based on a search on PubMed, there have only been 5 reported cases of triple synchronous primary cancers in the female genital tract. This case represents an extremely rare instance of triple synchronous primary cancers, comprising LCNEC arising from the LUS, along with endometrioid carcinomas simultaneously occurring in the UC and the right ovary, a combination that has not been previously reported. Such cases challenge our understanding of gynecologic oncology and underscore the importance of comprehensive histopathological and molecular analyses for accurate diagnosis and tailored therapeutic strategies. LCNEC of the endometrium is an exceptionally rare and aggressive tumor. It is characterized by rapid progression, high metastatic potential, and poor prognosis, regardless of treatment modality (Kobayashi et al., 2017). To the best of our knowledge, there are no reports of triple synchronous cancers in the female genital tract involving neuroendocrine carcinoma, nor are there any reports of neuroendocrine carcinoma arising in the LUS.

Most of what is known about LCNEC comes from the study of lung malignancies; but even so, LCNEC account for only 3 % of lung cancers. According to the WHO classification of pulmonary tumors, LCNEC is defined as large-cell carcinoma with neuroendocrine morphology (nesting, trabeculae, rosettes) expressing the neuroendocrine biomarkers synaptophysin, chromogranin A and/or CD56. Neuroendocrine tumors (NET) in gynecological organs are more common in the cervix and ovary and rarely in the endometrium. NETs of the endometrium include low-grade carcinoid tumors, high-grade small-cell neuroendocrine tumors (SCNEC), and LCNEC. The majority of these are SCNEC tumors (Jenny et al., 2019). However, the pathologic features of endometrial LCNECs closely resemble poorly-differentiated adenocarcinoma, undifferentiated sarcoma, and malignant mixed Mullerian tumor. Therefore, it is relatively difficult to differentiate these tumors preoperatively based on small biopsy specimens (Tu et al., 2018).

Little is known regarding the molecular features of endometrial NEC including how they compare to pulmonary NEC (the most common site for these neoplasms) and the more common endometrial carcinoma histotypes. Howitt et al. investigated the molecular alterations in 14 endometrial NEC using a targeted next generation sequencing panel (Oncopanel). Molecular analysis classified tumors into the 4 The Cancer Genome Atlas groups: (1) POLE-mutated/ultramutated (1/14; 7 %), (2) MSI/hypermutated (6/14; 43 %), (3) TP53 mutated/copy number high (2/14; 14 %), or (4) no specific molecular profile (5/14; 36 %). Overall, 50 % of cases were ultramutated or hypermutated. They reported that the molecular context may be important when selecting therapies for women with endometrial NEC, and immune checkpoint inhibition may be a reasonable approach to treatment of MSI-NEC (Howitt et al., 2020). Ono et al. analyzed 22 endometrial neuroendocrine carcinomas and 22 conventional endometrial neoplasia cases. Genetic analysis of hotspot mutations in 50 cancer-related genes revealed that the NEC group carried mutations in PIK3CA cases and PTEN, commonly encountered in endometrioid adenocarcinoma. Moreover, in six mixed-type NEC cases, next-generation sequencing, revealed several mutations common among NEC and endometrioid adenocarcinoma. They suggest that endometrial NEC could originate from conventional endometrial neoplasia, especially endometrioid adenocarcinoma (Ono et al., 2021).

Synchronous early-stage endometrioid endometrial carcinomas (EECs) and endometrioid ovarian carcinomas (EOCs) are associated with a favorable prognosis and have been suggested to represent independent primary tumors rather than metastatic disease (Schultheis et al., 2016). In this case as well, the endometrioid carcinomas of the endometrium and ovary is considered to have arisen independently and simultaneously in each location. But this case involves the third cancer, including LCNEC of the LUS, which has a poor prognosis, suggesting that the prognosis for this case is also likely to be poor. On the other hand, Sakamoto et al. evaluated blood and tissue samples from 17 patients of

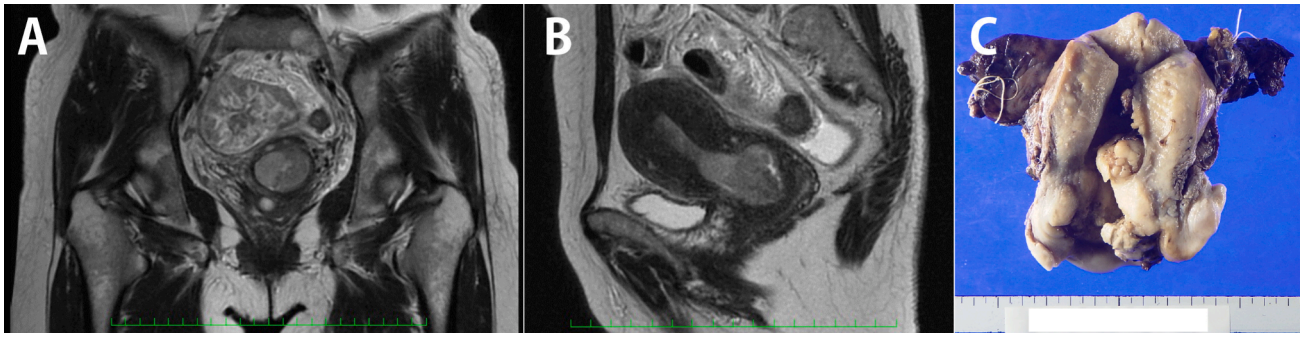

Fig. 1. Imaging data and macroscopic appearance of the surgical specimen. (A) Plain T2 weighted MRI image in frontal section showing the solid lesion of the right ovary and endometrium. (B) Plain T2 weighted MRI image in sagittal section showing the solid lesion of the lower uterine body through the upper cervix. (C) Macroscopic appearance of the uterus. The tumor is primarily located in the LUS and growing outward toward the cervix.

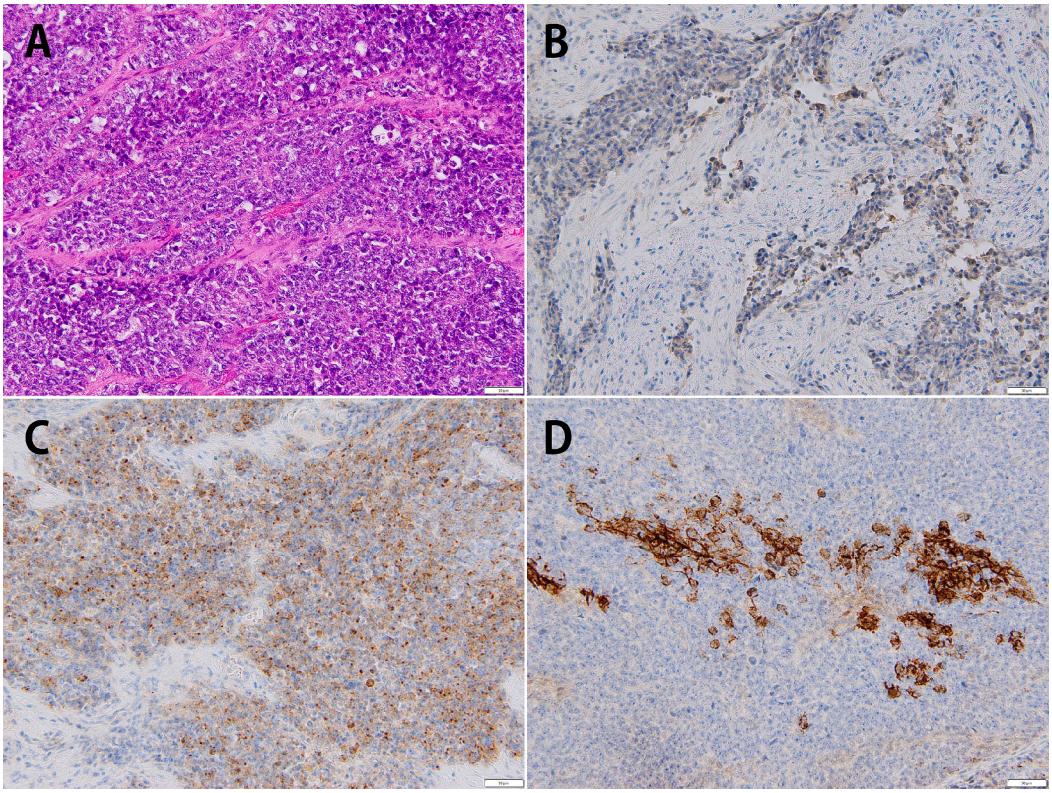

Fig. 2. Histological findings of LCNEC. (A) The tumor cells with increased chromatin and relatively prominent nucleoli proliferated forming irregular solid nests and infiltrative growth (H&E; original magnification, x200). (B-D) Immunohistochemical staining. The tumor cells were positive for (B) chromogranin, (C) synaptophysin, (D) CD56 (original magnification, x200).

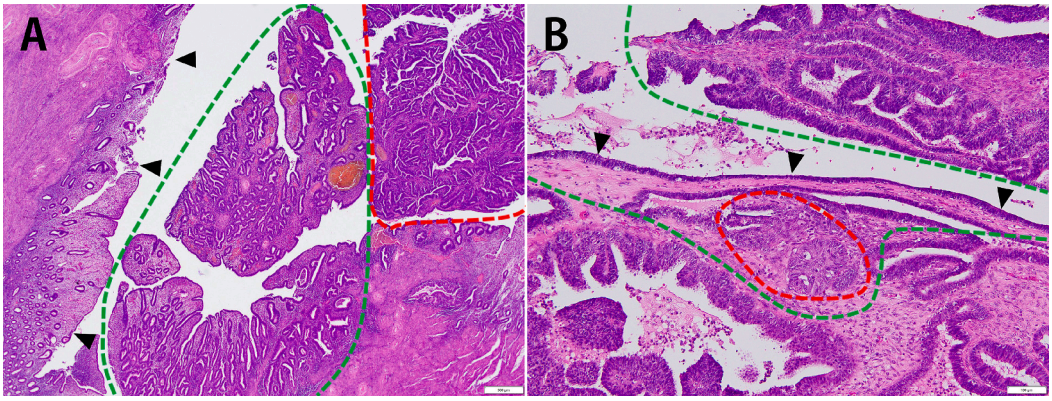

Fig. 3. Histological findings of endometrioid carcinoma of the endometrium and the right ovary. (A) The endometrioid endometrial carcinoma (red dot line) was considered to originate from the uterus due to the presence of atypical endometrial hyperplasia (green dot line) in the surrounding flat endometrium (black arrowhead) (original magnification, x20) (B) The endometrioid ovarian carcinoma (red dot line) was considered to be of ovarian origin, given the coexistence of borderline endometrioid tumors (green dot line) and endometriotic cysts (black arrowhead) (original magnification, x100). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

synchronous endometrial and ovarian cancers (SEOs) and analyzed the clonal origins of 41 samples from 17 patients by gene sequencing, mismatch microsatellite instability polymerase chain reaction assay and immunohistochemical staining of 4 repair genes. Based on the results, they concluded that most SEOs are likely to be a single tumor with metastasis instead of double primaries, and their origin could be endometrium. In addition, SEOs have a high frequency of mismatch repair gene abnormalities. These findings not only can support the notion of uterine primary, but also can help to expect the benefit for patients with SEOs by immuno-oncology treatment (Sakamoto et al., 2023) . Schulthesis et al. subjected sporadic synchronous EECs/EOCs patients to whole-exome massively parallel sequencing. Based on the results, they reported that sporadic synchronous EECs/EOCs are clonally related and likely constitute dissemination from one site to the other (Schulthesis et al., 2016). Whether these synchronous endometrial and ovarian cancers are two independent primary tumors or metastatic disease has important implications for prognostication and patient management (Zaino et al., 2001; Soliman et al., 2004). Molecular analyses are promising and hold great potential for accurate diagnosis, but it is necessary to gather more cases to ensure greater reliability.

The endometrium is pathologically divided into two regions: the uterine corpus proper (UC, the uterine body and fundus) and the lower

uterine segment (LUS, the isthmus of the uterus) (Hendrickson and Kempson, 1997). Endometrial cancer arises from the UC in many cases, but can also originate from the LUS in rare cases. When a tumor localized in the LUS expands macroscopically from the lower uterine body through the upper cervix, it is regarded as carcinoma of the LUS or isthmus (Jacques et al., 1997), and account for 3–8.1 % of all cases of endometrial cancer (Boronow et al., 1984; Hachisuga et al., 1989). In this case, the tumor was macroscopically confirmed to be localized to the lower uterine body and growing outward toward the cervix, leading to a diagnosis of carcinoma of the LUS. Endometrial neuroendocrine carcinomas (NECs) are aggressive carcinomas associated with an overall survival of 22 and 12 months in stages I–II and III–IV, respectively (Atienza-Amores et al., 2014; Park, 2022). Lynch syndrome (LS) is strongly associated with synchronous cancers of the endometrium and ovaries, and endometrial carcinoma of the LUS (Westin et al., 2008). We suspected a correlation between this case and LS, and the MSI test with the patient's consent was negative. This case represents an LCNEC of the LUS that has not been previously reported, highlighting the need to accumulate similar cases in the future to clarify details, including prognosis.

Maragliano et al. reported a comprehensive molecular study of a paradigmatic case of ovarian mixed neuroendocrine/non-neuroendocrine neoplasm (Ov-MiNEN) composed of a large cell ovarian neuroendocrine carcinoma (Ov-NEC) and a high-grade endometrioid carcinoma, associated with ovarian atypical endometriosis and endometrial atypical hyperplasia. Each neoplastic and preneoplastic component has been separately investigated and their results support a multistep carcinogenesis and a strong genetic relationship between the neuroendocrine and non-neuroendocrine components of the Ov-MiNEN. They demonstrated the substantial identity of the molecular profile of the two neoplastic components and their progression from a preexisting ovarian endometriotic lesion, in a patient with a coexisting preneoplastic proliferation of the endometrium, genotypically and phenotypically related to the ovarian neoplasm. They concluded this case represents a paradigm for the pathogenesis of high-grade neuroendocrine neoplasia in the ovary and supports the concept that NECs arise along the same pathogenetic pathways of autochthonous non-neuroendocrine carcinomas of each specific anatomical site, and moreover, this study supports the inclusion of MiNEN in the spectrum ovarian and, possibly, of all gynecological NENs, among which they are currently not classified (Maragliano et al., 2022). It is highly intriguing that this case, which involves the simultaneous occurrence of endometrioid carcinoma, atypical endometrial hyperplasia, and LCNEC in the endometrium, along with endometrioid carcinoma, borderline endometrioid tumors, and endometriotic cysts in the ovary, could be potentially closely related to Ov-MiNEN as defined by Maragliano et al.

According to previous reports, the treatment for LCNEC of the endometrium involves surgery followed by chemotherapy (etoposide and cisplatin (EP) or irinotecan and cisplatin (IP)) and locoregional radiation therapy (Du et al., 2021; Yang et al., 2024). Morizane et al. conducted a phase 3 randomized clinical trial comparing overall survival between EP and IP which are commonly used as community standard regimens for advanced NEC. Results of this randomized clinical trial demonstrate that both EP and IP remain the standard first-line chemotherapy options. Although adverse events (AEs) were generally manageable, grade 3 and 4 AEs were more common in the EP arm (Morizane et al., 2022). Postoperative 6 courses of chemotherapy with IP have been completed in this case. IP is also effective as first-line chemotherapy for ovarian cancer (Sugiyama et al., 2002). At ten months postoperatively, no signs of recurrence have been observed. Even if the initial response rate is high in early-stage disease, recurrence, distant metastasis, or progressive chemo-resistant disease frequently develop. Like LCNEC of the cervix, cyclophosphamide/doxorubicin/vincristine (CAV), irinotecan/platinum (IP), or topotecan can be considered as second-line therapies for endometrial LCNEC (Tu et al., 2018). Since the optimal treatment method remains unclear, it is necessary to accumulate case data and establish more definitive insights.

4. Conclusion

Comprehensive genomic and transcriptomic profiling could identify shared pathways and therapeutic targets, potentially improving outcomes in complex cases of multiple malignancies. The exploration of targeted therapies, such as immune checkpoint inhibitors, for LCNEC and molecular-targeted treatments for endometrioid carcinoma is warranted.

5. Consents

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

CRediT authorship contribution statement

Kaichiro Yamamoto: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Shin-ichi Nakatsuka:** Software, Investigation, Formal analysis. **Tomochika Goto:** Investigation, Data curation. **Reiko Samoto:** Investigation, Data curation. **Aki Minami:** Investigation. **Masatoshi Imamura:** Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Atienza-Amores, M., Guerini-Rocco, E., Soslow, R.A., et al., 2014. Small cell carcinoma of the gynecologic tract: a multifaceted spectrum of lesions. Gynecol. Oncol. 134, 410–418.

Boronow, R.C., Morrow, C.P., Creasman, W.T., et al. 1984. Surgical staging in endometrial cancer: Clinical-pathologic findings of a prospective study. Obstet. Gynecol. 63.825-832.

Du, R., Jiang, F., Wang, Z.-Y., et al., 2021. Pure large cell neuroendocrine carcinoma originating from the endometrium: a case report. World J. Clin. Cases. 9, 3449–3457.

Hachisuga, T., Kaku, T., Enjoji, M., 1989. Carcinoma of the lower uterine segment. Clinicopathologic analysis of 12 cases. Int. J. Gynecol. Pathol. 8, 26–35.

Hendrickson, M.R., Kempson, R.L. 1997. Normal histology of the uterus and fallopian tubes. Histology for pathologists. Lippincott-Raven Publishers. Philadelphia.

Howitt, B.E., Dong, F., Vivero, M., et al., 2020. Molecular characterization of neuroendocrine carcinomas of the endometrium representation in all 4 TCGA groups. Am. J. Surg. Pathol. 44, 1541–1548.

Jacques, S.M., Qureshi, F., Ramirez, N.C., et al., 1997. Tumors of the uterine isthmus: clinicopathologic features and immunohistochemical characterization of p53 expression and hormone receptors. Int. J. Gynecol. Pathol. 16, 38–44.

Jenny, C., Kimball, K., Kilgore, L., et al., 2019. Large cell neuroendocrine carcinoma of the endometrium: a report and review of the literature. Gynecol. Oncol. Rep. 28, 96–100.

Kobayashi, A., Yahata, T., Nanjo, S., et al., 2017. Rapidly progressing large-cell neuroendocrine carcinoma arising from the uterine corpus: a case report and review of the literature. Mol. Clin. Oncol. 6, 881–885.

Maragliano, R., Libera, L., Carnevali, I., et al., 2022. Mixed neuroendocrine/non-neuroendocrine neoplasm (MiNEN) of the ovary arising from endometriosis: molecular pathology analysis in support of a pathogenetic paradigm. Endocrine Pathology 33, 400–410.

Morizane, C., Machida, N., Honma, Y., et al., 2022. Effectiveness of etoposide and cisplatin vs irinotecan and cisplatin therapy for patients with advanced neuroendocrine carcinoma of the digestive system. JAMA. Oncol. 8, 1447–1455.

Ono, K., Kasajima, R., Katayama, K., et al., 2021. Clinicopathological and molecular characteristics of endometrial neuroendocrine carcinomas reveal preexisting endometrial carcinoma origin. Pathol. Int. 71, 491–499.

Park, H.K., 2022. Neuroendocrine carcinomas of the uterine cervix, endometrium, and ovary show higher tendencies for bone, brain, and liver organotrophic metastase. Curr. Oncol. 29, 7461–7469.

Pearce, C.L., Templeman, C., Rossing, M.A., et al., 2021. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 13, 385–394.

Sakamoto, I., Hirotsu, Y., Amemiya, K., et al., 2023. Elucidation of genomic origin of synchronous endometrial and ovarian cancer (SEO) by genomic and microsatellite analysis. J. Gynecol. Oncol. 34, e6.

Schultheis, A.M., Ng, C.K., De Filippo, M.R., et al. 2016. Massively Parallel Sequencing-Based Clonality Analysis of Synchronous Endometrioid Endometrial and Ovarian Carcinomas. J. Natl. Cancer Inst. 108(6).djv427.

Soliman, P.T., Slomovitz, B.M., Broaddus, R.R., et al., 2004. Synchronous primary cancers of the endometrium and ovary: a single institution review of 84 cases. Gynecol. Oncol. 94, 456–462.

Sugiyama, T., Yakushiji, M., Kamura, T., et al., 2002. Irinotecan (CPT-11) and cisplatin as first-line chemotherapy for advanced ovarian cancer. Oncology. 63, 16–22.

Tu, Y.-A., Chen, Y.-L., Lin, M.-C., et al., 2018. Large cell neuroendocrine carcinoma of the endometrium: a case report and literature review. Taiwanese J. Obstetr. Gynecol. 57, 144–149.

Westin, S.N., Lacour, R.A., Urbauer, D.I., et al., 2008. Carcinoma of the lower uterine segment: a newly described association with lynch syndrome. J. Clin. Oncol. 26, 5965–5971.

Yang, F., Liang, S., Liu, C., et al., 2024. Endometrial large cell neuroendocrine carcinoma: a case report and literature review. Gynecol. Oncol. Rep. 54, 101429.

Zaino, R., Whitney, C., Brady, M.F., et al. 2001. Simultaneously detected endometrial and ovarian carcinomas–a prospective clinicopathologic study of 74 cases: a gynecologic oncology group study. Gynecol. Oncol. 83.355–362.