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Mixed large and small cell neuroendocrine carcinoma and endometrioid carcinoma of the endometrium with high microsatellite instability: A case report and literature review

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Abstract

A 65-year-old, gravida 3, para 2 Japanese woman was referred to our hospital for symptomatic thickening of the endometrial lining. Endocervical and endometrial cytology revealed an adenocarcinoma. The endometrial biopsy specimen was mixed, with a glandular part diagnosed as endometrioid carcinoma and a solid part diagnosed as high-grade mixed large and small cell neuroendocrine carcinoma (L/SCNEC). She underwent extra-fascial hysterectomy with bilateral salpingo-oophorectomy, complete pelvic and para-aortic lymphadenectomy, and omentectomy (FIGO IIIB, pT3b pN0 M0). She currently has no deleterious germline mutation, but high tumor mutation burden and high microsatellite instability (MSI) were identified. She underwent six cycles of platinum-based frontline chemotherapy and achieved complete remission. Immune checkpoint blockade therapy is a promising second-line therapy for MSI-high solid tumors. However, the MSI or mismatch repair (MMR) status of endometrial L/SCNEC remains unclear in the literature. Universal screening for MSI/MMR status is needed, particularly for a rare and aggressive disease.

Keywords

Endometrial cancer, neuroendocrine carcinoma, DNA mismatch repair, microsatellite instability

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Introduction

Endometrial neuroendocrine carcinoma (Em-NEC) does not have an evidenced-based standardized frontline therapy yet owing to its rarity and aggressiveness. Based on the largest study using the National Cancer Database, Em-NEC accounts for 1.3% of all endometrial carcinomas, and the 5-year survival rate is 38.3% in all stages.[1] Patients with Em-NEC are currently treated with multimodal therapy combining surgery, chemotherapy, and radiation, according to the guidelines for endometrial cancer or studies on small cell lung carcinoma, because both the Japan Society of Gynecologic Oncology[2] and National Comprehensive Cancer Network[3] guidelines lack information on a standard therapy specific to Em-NEC.

Tumor mutation burden (TMB) is used as a surrogate for neoantigen load[4] and is assessed using gene panel testing. High-microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) are TMB subtypes that are assessed using a panel of microsatellite markers and immunohistochemical stains in the tumor tissues, respectively. A solid tumor with TMB-high/MSI-H/dMMR shows durable sensitivity to immune checkpoint blockade therapy. More than

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2% of endometrial cancers and neuroendocrine tumors independently show MSI-H/dMMR.[5] However, to date, there is a paucity of information regarding the MSI/MMR status of Em-NEC.

We herein report a case of mixed large and small cell neuroendocrine carcinoma (L/SCNEC) of the endometrium that was preoperatively presumed by endometrial biopsy, and provide a literature review regarding the MSI/MMR status of this entity.

Case

A 65-year-old, gravida 3, para 2, Japanese postmenopausal woman who complained of abnormal uterine spotting was referred to our hospital. She had no medical history and familial history of solid tumors in third-degree relatives. One month before referral, she visited a primary urologic clinic for sudden-onset hematuria. Transabdominal ultrasound demonstrated an intact urinary tract but revealed uterine enlargement and thickened endometrial lining. Contract-enhanced magnetic resonance imaging (MRI) revealed a 24 mm lesion protruding from the posterior endometrium (Figure 1(a)).

Upon initial examination at our department, transvaginal ultrasound demonstrated a 15-mm thick endometrium. Serum CA125, CA19-9, and hemoglobin levels were normal. Cervical, endocervical, and endometrial cytology revealed an adenocarcinoma, presumed to be an endometrial carcinoma. Her endometrial biopsy demonstrated an endometrial carcinoma with unknown grade combined with a high-grade neuroendocrine carcinoma based on the immunohistochemical staining profiles. The high-grade NEC component was also morphologically suspected to exist in combination with L/SCNEC. Contrast-enhanced computed tomography revealed no lymph node and distant metastatic lesions. She was preoperatively diagnosed with endometrial cancer, FIGO IA (T1a N0 M0).[6]

She underwent extra-fascial hysterectomy, bilateral oophorectomy, retroperitoneal (pelvic and aortic) lymphadenectomy, partial omentectomy, and additional low anterior resection due to intraoperative bowel injury. Intraoperative peritoneal cytology showed no malignancy. Macroscopic examination of the resected specimen showed a 55 mm tumor that had mainly developed from the posterior endometrium (Figure 1(b)). Microscopic examination revealed a grade 2 endometrioid carcinoma (Figure 1(c)) with histopathologic differentiation located within and adjacent to the uterine lumen, plus mixed L/SCNEC (Figure 1(d)) located outside and adjacent to the uterine serosa that partially invaded the parametrium. In the largest cross-sectional slice, the NEC component accounted for ~25%, while the endometrioid adenocarcinoma accounted for ~75%. Immunoreactivity for CD56 was more diffuse in the SCNEC (~100%) than that in the LCNEC (~90%; Figure 1(e)). Immunoreactivity for synaptophysin (~100% in the SCNEC and ~30% in the LCNEC; Figure 1(f)) and chromogranin A (~60% in the SCNEC and ~10% in the LCNEC; image not shown) was positive only in SCNEC. The tumor nuclear diameter in LCNEC (Figure 1(g)) was three times larger than the size of a small lymphocyte and was clearly distinguished from SCNEC (Figure 1(h)). She was finally diagnosed as FIGO IIIB (pT3a pN0 M0).[6] We retrospectively re-evaluated the preoperative cytology samples and found that there was a small number of scattered or clustered atypical cells, with a small shape and a high nucleocytoplasmic ratio in endocervical (Figure 2(a)) and endometrial cytology (Figure 2(b)), suggesting SCNEC.

Irinotecan hydrochloride was initiated at 60 mg/m^2 on days 1, 8, and 15, plus 60 mg/m^2 cisplatin on day 1 every 28 days as frontline chemotherapy. Her cancer gene mutations were screened after genetic counseling. Gene panel testing using the OncoGuide™ NCC Oncopanel System (National Cancer Center, Tokyo, Japan and Sysmex Corporation, Kobe, Japan) revealed 17 somatic mutations in the tumor, three germline mutations (*BRCA2, RB1, and MSH2*) in the peripheral blood, and high TMB. The tumor content rate in the sample was 80%, and most samples had an NEC component. All three germline mutations showed conflicting interpretations of pathology/uncertain significance. Additional MSI testing showed high results.[5] There was no evidence of disease 3 months after six cycles of chemotherapy, and the patient was shifted to active surveillance. All medical procedures described above were provided by the health insurance system in Japan. Written informed consent was obtained from the patient and the patient's husband for their anonymized information to be published in this article.

Discussion

This case has two major clinical implications. First, endometrial L/SCNEC could be preoperatively diagnosed by endometrial biopsy, and the patient had a good response to definitive surgical resection followed by six cycles of platinum-based frontline chemotherapy. Second, L/SCNEC demonstrated high-TMB without deleterious germline mutation but with high-MSI.

Table 1 summarizes the nine previous cases of endometrial L/SCNEC, reported in English, that were found in a search of PubMed/MEDLINE, as well as the present case. The average patient age at diagnosis was 65.2 years; eight of the cases were diagnosed at a later stage. All patients underwent definitive surgical resection followed by adjuvant therapies. The median follow-up time was 8.3 months, and the median survival was 24 months. Schlechtweg et al. examined 364 cases of Em-NEC in a 12-year period using the National Cancer Database and reported a median survival of 17 months, which was shorter than that of women with poorly differentiated endometrioid carcinoma (144 months).[1] Matsumoto et al.[7] reported that pure-type Em-NEC has a

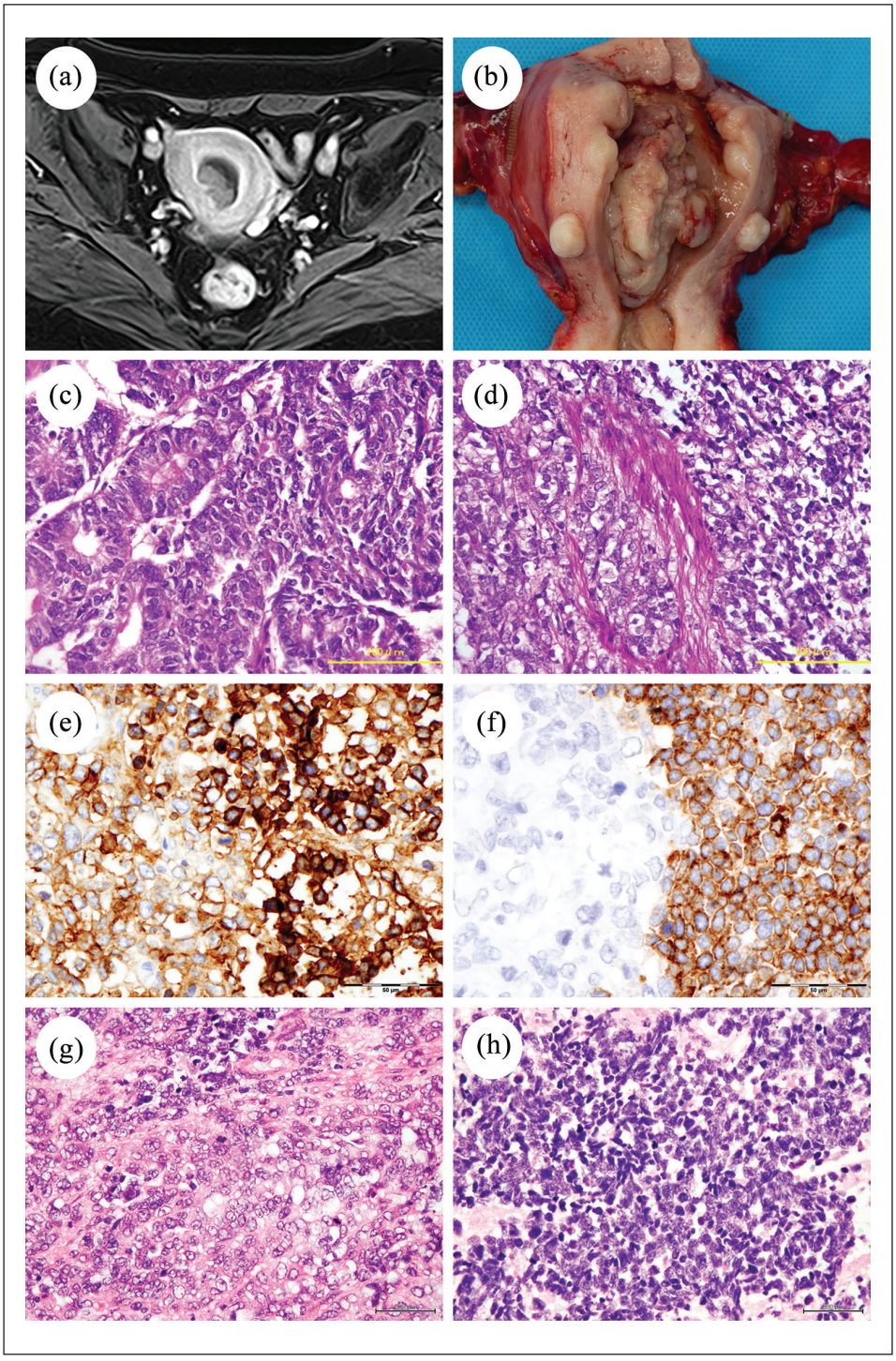

Figure 1. (a) Contrast-enhanced magnetic resonance imaging demonstrating a 24 mm lesion protruding from the endometrium and invading less than half of the myometrium. (b) Gross examination showing a 55 mm tumor that is mainly developing from the mid and posterior endometrium. (c) An endometrial gland-like architecture composed of severe atypical cells can be seen accompanied by approximately 30% of solid growth (hematoxylin and eosin stain). (d) A nested or diffuse architecture composed of ovoid cells with condensed chromatin and scant cytoplasm can be seen, accompanied by increased mitotic figures. These atypical cells morphologically resemble a lung small cell carcinoma and are morphologically divided into large (left) and small (right) cell components. (e) Small cell component displays a stronger immunoreactivity for CD56 than does large cell component. (f) Immunoreactivity for synaptophysin is positive only in small cell neuroendocrine carcinoma. (g) Representative image of large cell neuroendocrine carcinoma. (h) Representative image of small cell neuroendocrine carcinoma.

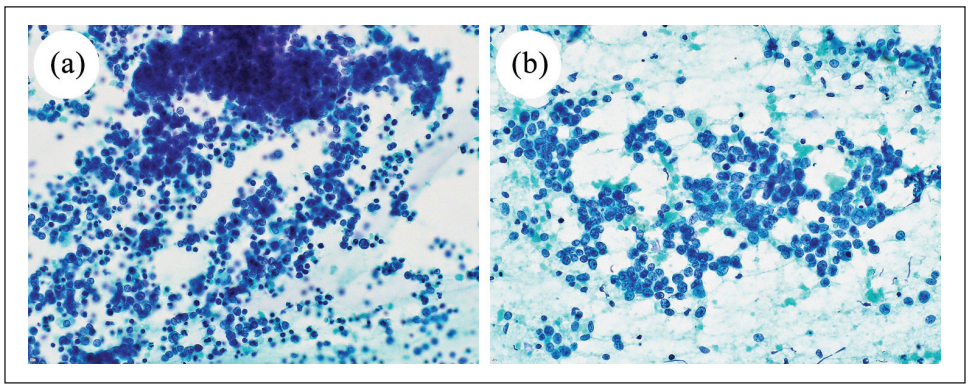

Figure 2. Scattered or clustered atypical cells with a small shape and a high nucleocytoplasmic ratio are seen on endocervical (a) and endometrial (b) cytology (Papanicolaou stain).

Table 1. Microsatellite instability status of the reported mixed large and small cell neuroendocrine carcinoma of the endometrium (modified from Hu et al.[8]).

Authors	Years	Case	Age (years)	Surgery	Stage	Pathology	MMR/MSI status[a]	Adjuvant Tx	Outcome, follow-up period
Mulvany et al.[9]	2008	1	88	TAH + BSO + PLA	IIIC	L/SCNEC + EC G3	NA	RT	AWD, 1 month
Pocrnich et al.[10]	2016	2	65	TAH + BSO + LND	IA	L/SCNEC + EC G3	Normal	RT	DOD, 9 months
(A series of 6 cases)		3	68	TAH + BSO	IIIA	L/SCNEC + EC G2	MLH1, PMS2 lost	PBCT + RT	NED, 24 months
		4	68	TAH + BSO + LND + App	IIIB	L/SCNEC + EC G3 + CCC	Normal	PBCT + RT	DOD, 13 months
		5	87	TAH + BSO	IVB	L/SCNEC + EC G3	NA	PBCT	DOD, 21 months
		6	55	TAH + BSO + App	IVB	L/SCNEC	Normal	PBCT	DOD, 3 months
		7	37	TAH + BSO	IVB	L/SCNEC	NA	PBCT	DOD, 2 months
Hu et al.[8]	2019	8	54	LRH + BSO + PLA + PAN	IIIC2	L/SCNEC + SC	NA	CCRT	AWD, 0 month
Present case	2020	9	65	TAH + BSO + PLA + PAN + OM	IIIB	L/SCNEC + EC G2	MSI-high	CPT-P	NED, 3 months

App: appendectomy; AWD: alive with disease; BSO: bilateral salpingo-oophorectomy; CCC: clear cell carcinoma; CCRT: concurrent chemoradiotherapy; CPT-P: irinotecan hydrochloride plus cisplatin; DOD: died of disease; EC: endometrioid carcinoma; G: grade; LND: lymphadenectomy (details unknown); L/SCNEC: large and small cell neuroendocrine carcinoma; LRH: laparoscopic radical hysterectomy; MMR: mismatch repair; MSI: microsatellite instability; NA: not applicable; NED: no evidence of disease; OM: omentectomy; PAN: para-aortic lymphadenectomy; PBCT: platinum-based chemotherapy; PLA: pelvic lymphadenectomy; RT: radiation therapy; SC: serous carcinoma; TAH: total abdominal hysterectomy; Tx: therapy.
[a]Analysis of the loss of expression of four MMR protein enzymes using immunohistochemistry or analysis of five tumor microsatellite loci using polymerase chain reaction-based assay (five mixed mononucleotide and dinucleotide loci (BAT25, BAT26, D2S123, D5S346, and D17S250).

significantly worse prognosis compared with mixed-type Em-NEC. Taking these findings together, the median survival in our cohort might be explained by the fact that seven of the nine cases were mixed-type L/SCNEC.

Immune checkpoint blockade therapy has durable clinical benefits for previously treated or metastatic MSI-H/dMMR, although these represent only 2% to 4% of all diagnosed cancer patients.[11] However, when only considering individuals with Em cancer, previous studies have reported that MSI testing identified MSI-H in 16% (17/109) of these patients and immunohistochemistry detected dMMR in 28% (42/129) of these patients.[12,13] The polarized distribution of the median survival, as shown in Table 1, implies that Em-NEC has a short response duration to existing frontline therapy but lacks an established second-line therapy after disease progression (three died due to the disease within one year, and three had more than one-year survival). Second-line therapy using pembrolizumab for recurrent Em-NEC is promising because 2 out 5 patients (40%) have MSI-H/dMMR, which is a relatively higher proportion than that of pan-cancer as well as Em cancer patients.[14] In the gastroenteropancreatic tract, Lou et al. retrospectively screened the MMR status via immunohistochemistry in 44 patients with mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN).[14] They revealed that MMR deficiency was significantly associated with a better prognosis, implying possible existence of elevated immune responses in patients with dMMR, which might be attributed to the increased number of mutation-associated neoantigens. Although it is difficult to

simply extrapolate this data to Em-NEC, because of organ-specific tumor size and growth speed, their report supports the clinical significance of MSI-H/dMMR detection in patients with Em-NEC.[15] Among the patients with MSI-H/dMMR solid tumors, Lynch syndrome (LS) has been identified in 16.3%.[16] The present case does not meet the revised Amsterdam II criteria or LS genetic testing criteria on the basis of individual/family history. In addition, germline mutation of *MSH2* was detected but had conflicting interpretations of pathology/uncertain significance based on existing database. High-TMB detected by gene panel testing led us to check the MSI/MMR status of this patient.

Conclusion

We reported a case of L/SCNEC of the endometrium in a woman who was successfully treated with definitive surgical resection followed by platinum-based chemotherapy. Although a deleterious germline mutation was not found in MMR-associated genes, the tumor showed high-TMB and high-MSI. To date, this is the first case of high-MSI Em-NEC diagnosed by MSI testing. Neuroendocrine carcinoma can occur at any location in the body. Immune checkpoint blockade therapy is promising for pan-cancer with MSI-H/dMMR. Universal screening for MSI/MMR status and further accumulation of cases are needed.

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Ethical approval

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Informed consent

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