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Neuroendocrine Carcinoma of the Endometrium: A Clinicopathologic Study of 25 Cases

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Abstract

Neuroendocrine carcinoma (NECa) of the endometrium is an uncommon tumor. In this study, we present the clinicopathologic features of 25 such cases. The patients ranged in age from 37 to 87 years (median, 57), and most commonly presented with vaginal bleeding. The tumors were either pure NECa (10) or mixed with other histotypes (15), most commonly endometrioid carcinoma. The NECas were large cell type (15), small cell type (4), or a mixture of both (6). NECa was under-recognized in 89% of referral/consultation cases. All tumors were positive for 1 neuroendocrine marker (chromogranin, synaptophysin, CD56). Additional immunohistochemical (IHC) studies were obtained in 18 cases, with positive results as follows: keratin cocktail (17), diffuse p16 (6), PAX-8 (6), CD117 (6), and TTF-1 (1). Mismatch repair protein expression by IHC was abnormal in 8 of 18 cases (6 MLH1/PMS2 loss; 1 MSH2/MSH6 loss; 1 MSH6 loss). According to FIGO staging, cases were distributed as follows: I (6), II (2), III (10), and IV (7). All patients underwent surgical treatment, and 20 patients received adjuvant therapy. Twelve patients died of disease (mean survival 12.3 months). Eleven patients were alive 5 to 134 months following diagnosis, including 7 who achieved a 5-year survival (3 stage I; 4 stage III). In summary, most of our endometrial NECas were large cell type, mixed with other histotypes, and under-recognized. These tumors tend to be PAX-8 negative and may be associated with microsatellite instability. The recognition of NECa may have an impact on the treatment of the patients affected by this disease. Although NECa usually has an aggressive behavior, 28% of our patients survived at least 5 years.

Keywords

Endometrium; Carcinoma; Neuroendocrine carcinoma; Small cell carcinoma; Immunohistochemistry; PAX-8; p16; DNA mismatch repair

INTRODUCTION

Neuroendocrine carcinoma (NECa) of the endometrium is an uncommon histologic subtype of endometrial cancer, and includes both small cell and large cell variants. The study of this entity has been limited by its rarity. Approximately 90 cases of endometrial small cell NECa

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(SCNECa) have been reported in the literature to date ^{1, 2}, all as case reports or as small case series. The two largest series that fulfill the current WHO diagnostic criteria for endometrial SCNECa had 10 and 16 patients, and are now more than 20 years old ^{3, 4}. Studies of endometrial large cell NECa (LCNECa) are even less common, with only 15 cases reported in the literature ^{5–14}. Although immunohistochemistry (IHC) related to neuroendocrine (NE) marker expression is available for most published cases of endometrial SCNECa and LCNECa, expression of other IHC markers has not been examined in a comprehensive fashion.

In this study, the largest case series to date, we present our experience with 25 cases of NECa arising in the endometrium with a purpose to describe the clinical characteristics, histopathologic and immunophenotypic features, and behavior of these rare tumors.

MATERIALS AND METHODS

Institutional Review Board approval was obtained prior to the initiation of this study. Twenty-five cases of NECa arising in the endometrium were retrieved from the files of the Department of Pathology at The University of Texas, MD Anderson Cancer Center (MDACC) covering a 15 year period (1999–2014). Twelve patients had their primary surgery performed at another hospital and were referred to MDACC for further treatment recommendations (i.e., referrals), and in 6 cases pathology material had been sent in consultation to our Pathology Department for a definitive diagnosis (i.e., consults). The remaining 7 patients had their primary surgery performed at MDACC. Both pure NECa and those associated with other histotype(s) were included in this study.

The diagnoses of SCNECa and LCNECa were made according to the WHO criteria for neuroendocrine tumors of the uterus ¹⁵. Briefly, SCNECa was recognized histologically as a tumor that resembled pulmonary small cell carcinoma (i.e., a tumor composed of cells with scant cytoplasm, a “salt and pepper chromatin pattern,” and nuclear molding). LCNECa was recognized by the following features: 1) the presence of polygonal cells with abundant cytoplasm and prominent nucleoli, 2) a NE growth pattern (i.e., organoid nesting, trabecular or cord-like growth), and 3) the expression of at least one NE immunomarker (chromogranin, synaptophysin, or CD56) in >10% of tumor cells. Other histotypes of endometrial cancer were diagnosed according to the WHO classification ¹⁵.

Clinical information was obtained from the patients’ charts or from their treating physicians. The following parameters were recorded: patients’ ages, clinical presentation, treatment, and follow-up. In all cases, pathology reports and all available original hematoxylin-and-eosin (H&E) stained slides were re-reviewed (1 to 49 slides per case; median, 5 slides). In addition, we re-reviewed all available original IHC stained slides. The following parameters were recorded: tumor size, histotype (SCNECa, LCNECa, mixed), lymph-vascular space invasion (LVSI), geographic necrosis, and mitotic index (MI). MI was obtained by counting 10 consecutive high power fields (HPFs) in the most mitotically active area of the tumor.

On 18 cases with available unstained slides or blocks, additional IHC stains were performed using the avidin-biotin method. These additional IHC stains included pankeratin cocktail

(AE1/AE3, 1:50, Dako, Carpinteria, CA; Cam5.2, 1:50, BD Biosciences, San Jose, CA; MNF116, 1:50, Dako), cytokeratin 18 (DC10, 1:50, Dako), PAX-8 (polyclonal, 1:100, Protein Tech, Chicago, IL), p16 (E64H, 1:3 of pre-dilute, Ventana, Tuscon, AZ), CD117 (polyclonal, 1:100, Dako), TTF-1 (8G7G3/1, 1:20, Dako), MLH1 (G168-728, 1:300, Cell Marque, Rocklin, CA), PMS2 (A16-4, 1:125, BD Biosciences), MSH2 (FE11, 1:100, Calbiochem, San Diego, CA), and MSH6 (44, 1:300, BD Biosciences). In situ hybridization for Human papillomavirus (HPV) types 16, 18, 31, 33, and 51 (ENZ-32882, pre-dilute, Enzo Life Solutions, Farmingdale, NY) was also performed. IHC stain results were assessed semiquantitatively as follows: negative (no cells stained), focally positive (10% cells stained), patchy positive (11% to 49% cells stained) and diffusely positive (50% of cells stained). Of note, in most cases the IHC studies were obtained from blocks that contained the NECa component exclusively.

In a subset of cases that demonstrated mismatch repair (MMR) protein expression abnormalities, the H&E stained slides were re-reviewed to assess for the presence or absence of tumor-infiltrating lymphocytes. The clinical record was also re-reviewed for any history of previous or concurrent malignancies in the patient and close family members.

The International Federation of Gynecology and Obstetrics (FIGO) classification¹⁶ was used for staging.

RESULTS

The clinicopathologic features of the 25 cases in this study are summarized in Table 1. The patients' ages ranged from 37 to 87 years (median, 57; mean, 61). Presenting symptoms were known for 21 patients, and included vaginal bleeding (15), vaginal bleeding with abnormal Pap smear (2), vaginal bleeding with abdominal pain (1), abnormal Pap smear only (1), and symptoms related to metastases (2).

Gross tumor measurements were available in 19 cases, with maximum tumor dimension ranging from 0.8 cm to 12 cm (median, 6.0 cm). Microscopically, the NE component showed large cell morphology in 15 cases (Figure 1), small cell morphology in 4 cases (Figure 2), and both large and small cell morphology in 6 cases. In the latter 6 cases, the LCNECa component predominated. The cases of SCNECa were characterized predominantly by a diffuse growth pattern, with nests and cords comprising only a minor component. Pseudorosettes were infrequent, and no true rosettes or Homer Wright rosettes were seen. For the cases of LCNECa, the most common growth pattern was insular (organoid nesting) with admixed solid (diffuse) pattern. Trabecular or ribbon-like growth was less commonly observed. Ten tumors were pure NECa, whereas the remaining 15 cases were associated with 1 or more additional histotypes (13 conventional endometrioid carcinoma, ranging from FIGO grade 1 to 3; 1 serous carcinoma; and 1 conventional endometrioid carcinoma mixed with clear cell carcinoma) (Figure 3). In mixed cases, the NECa component accounted for 10–95% of the tumor volume (median, 80%). In 4 cases, bizarre multinucleated cells were observed within the LCNECa component. LVSI was present in 23 cases; the 2 cases without LVSI were low FIGO stage (IA and IB,

respectively). Geographic necrosis was identified in 21 cases. The MI was high for all cases, ranging from 17 to 128 mitoses per 10 high power fields (median, 31).

Sixteen of 18 referral/consultation cases were initially diagnosed as follows: grade 3 endometrioid carcinoma (9 cases), undifferentiated carcinoma (3 cases), primitive neuroectodermal tumor (2 cases), atypical carcinoid (1 case), and carcinosarcoma (1 case). In the remaining two referral/consultation cases, the original diagnosis and the second opinion diagnosis were concordant.

IHC staining results are summarized in Table 2. NE markers were performed as part of the initial diagnostic work-up of all 25 cases. All tumors were positive for at least one NE marker (chromogranin, synaptophysin or CD56) in >10% of neoplastic cells. There were 9 cases positive for only 1 NE marker, 11 cases positive for 2, and 5 cases positive for all 3 markers of NE differentiation. Of the 9 cases that showed patchy or diffuse staining with only 1 NE marker, immunopositivity was most commonly seen with synaptophysin (5/9 cases), followed by chromogranin (3/9 cases) and CD56 (1/9 cases). The tumor that stained for CD56 exclusively was a case of mixed LCNECa and FIGO grade 2 endometrioid carcinoma, and the diffuse and strong CD56 staining was detected only in the area showing the histological features diagnostic of LCNECa and not in the endometrioid component. The 11 cases that showed the expression of 2 NE markers were more commonly positive for synaptophysin and chromogranin as follows: 4 were cases were diffusely positive for both, 2 cases were diffusely positive for synaptophysin while patchy positive for chromogranin, 1 case was patchy positive for both, and 1 case was focally positive for synaptophysin while patchy positive for chromogranin. Three cases had expression of synaptophysin and CD56 as follows: 2 cases diffusely positive for synaptophysin had either diffuse or focal expression of CD56, and one case showed patchy positivity for both markers. The pattern of expression in the 5 cases positive for all 3 NE markers was as follows: 2 cases had diffuse expression of 2 NE markers (either synaptophysin/chromogranin or chromogranin/CD56) with patchy expression of a 3rd NE marker (CD56 or synaptophysin, respectively), 1 case had patchy expression of all 3 NE markers, and 2 cases had diffuse expression of CD56 with patchy expression of synaptophysin and either patchy or focal expression of chromogranin.

In addition, pankeratin and keratin 18 were expressed in 17 of 18 cases, with both markers showing similar staining in most cases (i.e. either diffusely or patchy positive), except in 2 cases where the expression of keratin 18 was detected in a larger number of neoplastic cells. Positivity for p16 was observed in 16 of 18 cases, in either a patchy (10) or a diffuse (6) distribution. In situ hybridization for high risk HPV (HRHPV) was performed in 5 of 6 cases demonstrating a diffuse p16 staining pattern, and no HRHPV was found in these cases. Only 6 of 18 cases were positive for PAX-8 and CD117. Focal TTF-1 positivity was observed in 1 case only.

IHC staining for the DNA mismatch repair (MMR) proteins MLH1, PMS2, MSH2 and MSH6 was also performed in 18 cases. These stains were obtained on blocks containing the NECa component only; as the cases were mostly referrals/consultations, additional blocks could not be obtained to test the MMR protein expression in the non-NECa component of mixed cases. Six cases showed loss of MLH1/PMS2, 1 case showed MSH2/MSH6 loss, and

1 case showed only MSH6 loss. Of these 8 cases with MMR protein expression abnormalities, the NE component showed large cell morphology in 6 cases, small cell morphology in 1 case, and a combination of large and small cell morphology in 1 case. NECa was the only carcinoma component in 4 cases, whereas in the remaining 4 cases the NECa was mixed with endometrioid carcinoma. Tumor-infiltrating lymphocytes were observed in 2 of the 8 cases. The patients with abnormal MMR protein expression ranged in age from 52 to 85 years (median, 64.5) at diagnosis. The mother of one patient with MLH1/PMS2 loss had been diagnosed with colorectal carcinoma in her 70s. None of the 8 patients met Amsterdam criteria for Lynch syndrome, although a thorough family history was not available for review in all cases.

Eight patients presented with early FIGO stage disease (stage IA, 3; stage IB, 3 and stage II, 2,) and 17 patients presented with advanced FIGO stage disease (stage IIIA, 3; stage IIIB, 4; stage IIIC1, 1; stage IIIC2, 2; stage IVB, 7).

No patient received neoadjuvant therapy, although 2 patients had received systemic chemotherapy in the past for the diagnoses of either peritoneal neoplasia not further specified or breast carcinoma. All 25 patients underwent hysterectomy (total, 21; total but morcellated, 2; supracervical, 1; and radical, 1) and bilateral salpingo-oophorectomy. Other procedures included: lymphadenectomies (14 cases), peritoneal and/or omental biopsies (6 cases), and appendectomies (2 cases). Information pertaining to post-operative therapy was available for 20 patients, of whom 11 received a combination of radiation therapy and platinum-based chemotherapy. Three patients received radiation therapy alone and 4 received chemotherapy alone (3 with a platinum-based regimen; 1 unknown). Two patients received no adjuvant therapy.

Survival data was available for 5 of 6 patients with stage I disease, of whom 3 were alive and without evidence of disease after a follow-up of 71, 96 and 118 months, respectively; 1 experienced recurrences at 8 and 23 months after initial diagnosis and was alive and without evidence of disease at 37 months; 1 died of disease at 9 months (stage IA). Of the 2 patients with stage II disease, 1 was alive with disease 11 months following diagnosis and 1 died of disease at 15 months. Survival data was available for 9 of 10 patients with stage III disease, of whom 4 were alive with no evidence of disease at follow-up periods of 66, 92, 120, and 134 months, including one patient who had experienced a recurrence at 25 months. Two patients were alive with no evidence of disease at shorter follow-up periods of 5 and 24 months, and 3 patients died of disease at 6 months, 13 months and 19 months. All 7 patients who presented with stage IVB disease died of disease at 2 to 35 months after diagnosis (median, 9 months).

DISCUSSION

In our study, endometrial NECa presented in patients with a wide age range (37 to 87 years; median, 57) with predominance in the sixth and seventh decades, as previously reported^{3, 4}. While vaginal bleeding was the most frequent presentation, two patients presented with symptoms related to extra-abdominal metastasis (dizziness due to brain metastasis and dyspnea secondary to lung metastasis), which has not previously been reported in

endometrial NECa. None of our patients presented with a paraneoplastic syndrome, of which at least 4 cases of visual paraneoplastic retinopathy^{17–20} and 1 case of Cushing's syndrome²¹ have been described in the literature. Although most previously published studies of endometrial NECa have not provided maximum tumor dimensions, both large bulky tumors and tumors confined to polyps have been described. The tumors in this series tended to be large, with a median size of 6 cm. We found that the most common form of NECa in this study was the large cell type, detected in 84% of our cases. This finding was somewhat unexpected, given the overwhelming predominance of reports of endometrial SCNECa over LCNECa in the published literature. As most of our cases represented either referrals or consults, a selection bias may explain this difference. Also, LCNECa is most likely under-reported due to its tendency to be associated with other histotypes of endometrial cancer which can make its recognition somewhat difficult. This common association of NECa with other histotypes of endometrial cancer has been reported by other investigators. Both Huntsman *et al.*⁴ and van Hoesen *et al.*³ found that 50% and 80%, respectively, of SCNECa were mixed with another histotype, and in the largest series of endometrial LCNECa by Mulvany and Allen⁵, 4 of 5 cases were mixed with an endometrioid carcinoma component.

Regarding the immunohistochemical profile of our cases, synaptophysin was the most commonly expressed neuroendocrine marker. This finding is in concordance with the results of others; on review of 17 cases of SCNECa^{3, 6, 20, 22–29} and 14 cases of LCNECa^{5–13} where both synaptophysin and chromogranin IHC were obtained, synaptophysin was slightly more sensitive than chromogranin. The expression of chromogranin in the absence of synaptophysin expression was noted in only 12% of our cases. Only one case in this series had CD56 staining as the sole IHC marker of NE differentiation. This case had the histological features of LCNECa as described in the Material and Methods section, thus eliminating the possibility of over-diagnosis of NECa based only on the expression of this marker. We acknowledge concerns that CD56, a neuroendocrine marker of tumors arising at many anatomical sites, may be a non-specific marker of NE differentiation in the gynecological tract due to its propensity to stain conventional endometrioid carcinomas of the endometrium³⁰ and ovary³¹. At this point, it is important to emphasize that the value placed on the expression of NE markers in the diagnosis of NECa varies according to the morphology. SCNECa can be designated as such as long morphological features resembling small cell carcinoma of the lung are displayed (i.e. the expression of NE markers is not required). In contrast, the diagnosis of LCNECa requires the expression of at least one NE marker, in addition to the presence of the histological features associated with NE differentiation (i.e. nesting, trabecular or ribbon-like formations). Of note, synaptophysin has been found to be expressed in up to 21% of endometrioid carcinomas and in up to 13% of serous carcinomas³².

Most studies published on endometrial NECa have demonstrated keratin positivity in tumor cells, but keratin negative cases have been reported^{3, 4, 9, 10, 24, 26} and are encountered in routine practice. In our series, 17 of 18 cases were positive with both a sensitive pankeratin cocktail and with keratin 18, most commonly in a patchy or diffuse distribution. The one case negative for both pankeratin and keratin 18 antibodies was diffusely positive for chromogranin, synaptophysin and CD56. In two cases, keratin 18 labeled more extensively

than pankeratin. We also encountered one case that was pankeratin negative and keratin 18 positive according to the outside pathology report. Shahabi *et al.*¹⁰ also reported one case of LCNECa negative for keratin AE1/AE3 but positive for keratin 18. Thus, keratin 18 may be slightly more sensitive than pankeratin in endometrial NECa, although the added value of keratin 18 may not be as great as for undifferentiated carcinomas^{33–35}.

It is known that p16 is usually diffusely and strongly positive in cervical adenocarcinomas of both usual and neuroendocrine types^{36, 37}, and in cases of high grade endometrial carcinomas, such as serous carcinoma³⁸ and a subset of undifferentiated carcinomas^{35, 39}. In cases of NECa arising in the endometrium, diffuse p16 positivity has already been reported in 3 cases of SCNECa^{6, 28} and 4 cases of LCNECa^{5, 13}, and patchy p16 positivity in 1 case of LCNECa⁶. Other case reports of p16 expression in SCNECa exist but do not specify diffuse versus patchy staining^{25, 40}. In this series, we confirmed that p16 is frequently positive in endometrial NECa (89% of our cases); however, in more than half of these cases, p16 was patchy positive rather than diffuse. Thus, patchy p16 positivity may point toward an endometrial origin, although diffuse p16 positivity may occur in NECa of both cervical and endometrial origin. In cases with diffuse p16 staining, in situ hybridization for high risk HPV and correlation with clinical and gross impression may be necessary to distinguish a cervical from endometrial primary. TTF-1 may potentially be of some use for distinguishing cervical NECa from endometrial NECa. In contrast to the uterine cervix where NECa are frequently TTF-1 positive³⁷, we found that TTF-1 positivity in endometrial NECa was rare. Previous studies of endometrial NECa had also failed to demonstrate TTF-1 immunoreactivity in two cases of endometrial SCNECa^{21, 41} and one case of LCNECa¹⁰.

PAX-8 is commonly expressed in epithelial cells of the gynecological tract, and most endometrial adenocarcinomas are PAX-8 positive by IHC⁴². Negative staining for PAX-8 was previously documented in one case report of endometrial LCNECa¹², but otherwise PAX-8 immunohistochemistry has not been examined in endometrial NECa. We found that only 33% of our cases were PAX-8 positive, suggesting that PAX-8 may not be a reliable marker of endometrial origin when evaluating a NECa of unknown primary at a metastatic site.

Overexpression of CD117 has been demonstrated in pulmonary SCNECa^{43, 44}, and this protein has also been shown to be overexpressed in a minority of cervical SCNECa^{45, 46}. Enthusiasm for detection of CD117 overexpression by IHC has waned somewhat since clinical trials have failed to demonstrate a benefit for imatinib therapy in pulmonary SCNECa with CD117 overexpression by IHC^{47, 48}. As has previously been reported in cervical NECa, we found that CD117 overexpression was infrequent (33%) in endometrial NECa, with only 1 case showing diffuse overexpression by IHC.

In this series, MMR protein expression by IHC was abnormal in 44% of cases tested, including MLH1/PMS2 loss, MSH2/MSH6 loss, and MSH6 loss only. Although MLH1/PMS2 loss may be attributable to sporadic MLH1 promoter hypermethylation, the latter two staining patterns are suggestive of Lynch syndrome. To our knowledge, this is the first study to demonstrate MMR protein expression abnormalities in NECa of the endometrium. Studies of SCNECa in the colorectum have demonstrated intact MMR proteins in most cases

⁴⁹; no equivalent studies of colorectal LCNECa have been undertaken. The fact that undifferentiated carcinoma of the endometrium is also known to be associated with MMR protein abnormalities ^{33, 50} and that undifferentiated carcinoma is a histologic mimic of LCNECa raises the possibility of misdiagnosis. We believe that all 8 cases with MMR protein expression abnormalities in this study truly met diagnostic criteria for NECa. In 1 case, the tumor had clear SCNECa morphology, which is histomorphologically distinct from undifferentiated carcinoma. In the 7 LCNECa cases, we appreciated both the presence of a NE growth pattern and diffuse positivity for at least 1 NE marker, well beyond the 10% threshold required by the WHO.

NECa can represent a diagnostic challenge, as seen in 89% of our referral/consult cases where there was diagnostic disagreement with the original diagnosis. In some cases, under-recognition of the NECa component was likely due to its association with a conventional endometrioid carcinoma. In most cases, a distinct high grade component was recognized but was originally interpreted as the solid component of endometrioid carcinoma, undifferentiated carcinoma, the sarcomatoid component of carcinosarcoma, or as primitive neuroectodermal tumor (PNET). In one case, the NECa was originally diagnosed as carcinoid tumor.

LCNECa is distinguished from FIGO grade 3 endometrioid carcinoma based on the presence of polygonal cells arranged in nests, trabecular or ribbon-like structures, and the expression of at least one NE marker. In contrast, the solid areas of FIGO grade 3 endometrioid carcinoma do not show this distinct histological appearance. As indicated above, the expression of NE markers alone is not enough to distinguish these two tumors.

The distinction of LCNECa from undifferentiated carcinoma is somewhat arbitrary, and is based solely on the percentage of tumor cells expressing at least one NE marker (synaptophysin, chromogranin, CD56 in >10% of tumor cells) ¹⁵. The histological features of these tumors are similar, and although one study of undifferentiated carcinomas allowed for diffuse NE marker positivity ⁵¹, in compliance with the current WHO classification we think that expression of NE markers greater than 10% should prompt the use of the term LCNECa. It should be acknowledged, however, that some other authors have proposed that this diagnosis should require the expression of two NE markers and/or >20% positivity ^{33, 52} and that some gynecologic pathologists may be reluctant to recognize CD56 positivity as diagnostic of NE differentiation ^{5, 51}. Although the extent of expression of keratin cocktail and keratin 18 was thought to be useful in the distinction of an undifferentiated carcinoma from an endometrial NECa, a recent study from our group demonstrated that contrary to previous reports, undifferentiated carcinoma of the endometrium can be diffusely positive for keratin cocktail or keratin 18 in up to 33% and 41% of the cases, respectively ³⁵. Therefore, the extent of expression of these keratins cannot reliably be used to make this distinction. Of interest, p16 diffuse expression is detected in about 30% of cases of both undifferentiated carcinoma ³⁵ and NECa. Something similar occurs with the expression of PAX-8, which is lost in approximately 80% of the cases of undifferentiated carcinoma ³⁵ and in 67% of the cases of NECa.

Other entities that may be confused with NECa are carcinosarcoma, PNET and carcinoid tumor. We encountered one case where, due to the close association of conventional adenocarcinoma and small cell carcinoma, the latter was mistaken for a sarcomatoid component. Attention to the histological features should allow for the correct diagnosis. PNET is a classic, albeit rare, differential for NECa. PNETs, in contrast to NECa, frequently show evidence of neuroectodermal differentiation (fibrillary background, rosettes, ganglion cells, astrocyte-like cells) and are negative for cytokeratins⁵³. Although PNETs are commonly synaptophysin positive, these tumors are typically chromogranin negative⁵³. Thus, chromogranin positivity may point towards a diagnosis of NECa in the rare instance of keratin negative NECa, highlighting the importance of performing a full NE IHC panel. Finally, we encountered one case of LCNECa initially diagnosed as carcinoid tumor, which is a very rare tumor in the endometrium with poorly established diagnostic criteria. This particular case lacked geographic necrosis, but the presence of cytologic atypia, numerous apoptotic bodies and an elevated MI in excess of 20 per 10 high power fields were in keeping with the diagnosis of LCNECa.

Most (68%) of our cases presented with FIGO stage III or IV disease. In a recent review of SCNECa of the gynecologic tract², the ratio of advanced to early stage disease for endometrial NECa was 1.3:1. On evaluation of 14 published cases of LCNECa with staging information available^{5-11, 13, 14}, the ratio of advanced to early stage disease in that setting was 1.8:1. It is possible that the greater number of advanced stage cases in our series (2.1:1) reflects that this is the largest collection of cases to date and/or that the cases are collected from a referral patient population. Of 25 patients in our series, 12 women died of disease (1 FIGO stage I, 1 FIGO stage II, 3 FIGO stage III, 7 FIGO stage IV) with a mean survival of 12.3 months. Of interest, 7 patients (5 LCNECa and 2 SCNECa) survived at least 5 years, including 4 patients with FIGO stage III disease, one of whom had experienced a recurrence at 25 months. The other 3 patients who had a long term survival presented with FIGO stage I disease. Most of the tumors in these patients who have survived at least 5 years showed a dominant NECa component, accounting for 70% to 100% of the neoplasms, with a single case composed of 50% SCNECa and 50% endometrioid carcinoma, FIGO grade 1. Our findings regarding the clinical behavior of NECa of the endometrium are in agreement with previous reports, in that most cases behave aggressively^{2-5, 10, 11, 13, 14, 23, 26, 27, 29, 54, 55}; however, in a subset of cases the disease responds to surgical and adjuvant therapy. Of note, previous reports of endometrial NECa surviving more than 5 years have been of small cell type^{6, 26, 54, 56} but there are no similar reports in LCNECa.

In summary, NECa arising in the endometrium is a rare disease. Most of the cases in this cohort were large cell type and mixed with other histotypes. NECa tends to be under-recognized, which may have therapeutic implications; although a thorough review of treatment modalities was not a goal of this study, we observed in several instances that etoposide was added to the usual platinum-based chemotherapeutic regimen when a NECa component had been reported. Endometrial NECa is typically positive for keratin cocktail, keratin 18 and synaptophysin. Diffuse p16 positivity, as seen in NECa arising in the cervix, may occasionally occur and this represents a potential diagnostic pitfall. In addition, these tumors are usually PAX-8, TTF-1, and CD117 negative. Of interest, MMR protein

abnormalities may be seen in almost 50% of tumors. Although most tumors behave aggressively, there is a subset of patients who may achieve a 5-year survival.

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Figure 1.

Endometrial large neuroendocrine carcinoma demonstrating trabecular and solid growth patterns [A], organoid growth pattern with geographic necrosis [B], peri-lobular pseudopalisading [C], and synaptophysin immunopositivity [D]. (Hematoxylin-eosin, original magnification 4× [A], 4× [B] and 10× [C]; original magnification 10× [D]).

Figure 2. Endometrial small cell neuroendocrine carcinoma at low [A] and high power [B] demonstrating neoplastic cells of small to intermediate size, with high nucleus to cytoplasm ratio, salt-and-pepper like chromatin distribution, nuclear molding, and frequent mitotic figures and apoptotic bodies. (Hematoxylin-eosin, original magnification 10× [A] and 40× [B]).

Figure 3. Mixed carcinomas composed of neuroendocrine carcinoma and endometrioid adenocarcinoma [A] and serous carcinoma [B]. (Hematoxylin-eosin, original magnification 4× [A] and 10× [B]).

Clinicopathologic Features of 25 Cases of Neuroendocrine Carcinoma of the Endometrium

Table 1

CaseNo.	Pt Age (yrs)	Presenting Symptom	Histology	% NE Component	Tumor Size (cm)	FIGO Stage	Surgical Treatment	Adjuvant Therapy	Follow Up
1	46	NA	SCNECa + ECa G1	50	2.1	IA	HystBSO	NA	NED, 71 mo
2	54	NA	LCNECa	100	0.8	IA	HystBSO	xRT	NED, 96 mo
3	65	Bleeding	LC/SCNECa + ECa G3	80	4.5	IA	HystBSO, LND	xRT	DOD, 9 mo
4	84	Bleeding, Abnormal Pap	LCNECa + ECa G2	90	2.8	IB	HystBSO, LND	xRT	NED, 118 mo
5	66	Bleeding	LCNECa + ECa G2	40	7.5	IB	HystBSO, LND	Chem, xRT	Recurrences at 8 mo & 23 mo; current status NED, 37 mo
6	55	Bleeding	LCNECa + ECa G2	90	4.5	IB	HystBSO	NA	NA
7	47	Bleeding	LCNECa + ECa G2	50	6.0	II	HystBSO, LND	Chem, xRT	DOD, 15 mo
8	51	Bleeding, Abnormal Pap	LCNECa + ECa G2	60	7.0	II	HystBSO, LND, Obx	Chem, xRT	AWD, 11 mo
9	53	Bleeding	SCNECa + ECa G3	85	8.9	IIIA	HystBSO, LND	Chem, xRT	DOD, 19 mo
10	68	Bleeding	LC/SCNECa + ECa G2	95	6.0	IIIA	HystBSO	Chem, xRT	NED, 24 mo
11	69	Bleeding	LCNECa	100	NA	IIIA	HystBSO, LND	Chem, xRT	NED, 5 mo
12	59	Abnormal Pap	LCNECa + SCa	90	NA	IIIB	HystBSO, LND	Chem, xRT	NED, 92 mo
13	54	Bleeding	LCNECa + ECa G2	70	2.7	IIIB	HystBSO, LND	Chem, xRT	NED, 134 mo
14	57	NA	SCNECa	100	8.0	IIIB	HystBSO, LND	Chem	NED, 120 mo
15	68	Bleeding	LC/SCNECa + ECa G3 + CCCa	80	7.5	IIIB	HystBSO, LND, App	Chem, xRT	DOD, 13 mo
16	52	Bleeding	LCNECa	100	5.5	IIIC1	HystBSO, LND	Chem, xRT	Recurrence at 25 mo; current status on therapy with NED, 66 mo

CaseNo.	Pt Age (yrs)	Presenting Symptom	Histology	% NE Component	Tumor Size (cm)	FIGO Stage	Surgical Treatment	Adjuvant Therapy	Follow Up
17	55	Bleeding	LCNECa	100	Entire uterus	IIIC2	HystBSO, LND	None	DOD, 6 mo
18	63	NA	LCNECa	100	9.0	IIIC2	HystBSO, LND, Obx	NA	NA
19	87	Bleeding	LC/SCNECa + ECa G3	10	4.0	IVB	HystBSO, Obx	Chem	DOD, 21 mo
20	59	Dizziness (brain metastasis)	LCNECa + ECa G2	50	NA	IVB	HystBSO, LND	Chem, xRT	DOD, 12 mo
21	55	Bleeding, Abdominal pain	LC/SCNECa	100	Entire uterus	IVB	HystBSO, App, STbx	NA	DOD, 3 mo
22	85	Bleeding	SCNECa + ECa G2	90	7.0	IVB	HystBSO	NA	DOD, 35 mo
23	37	Bleeding	LC/SCNECa	100	6.2	IVB	HystBSO, Obx, Pbx	Chem	DOD, 2 mo
24	80	Dyspnea (lung metastasis)	LCNECa	100	NA	IVB	HystBSO, Pbx	None	DOD, 3 mo
25	55	Bleeding	LCNECa	100	12.0	IVB	HystBSO, LND, Obx	Chem	DOD, 9 mo

Abbreviations: **App**, appendectomy; **AWD**, alive with disease; **CCCa**, clear cell carcinoma; **Chem**, chemotherapy; **DOD**, died of disease; **ECa**, endometrial endometrioid carcinoma; **G**, grade; **HystBSO**, hysterectomy with bilateral salpingo-oophorectomy; **LND**, lymph node dissection; **NA**, not available; **NED**, no evidence of disease; **Obx**, omental biopsy; **Pbx**, peritoneal biopsy; **SCa**, serous carcinoma; **STbx**, soft tissue biopsy; **xRT**, radiation therapy

Table 2

Immunohistochemical Staining Results in Neuroendocrine Carcinoma of the Endometrium

Case No.	SYN	CHG	CD 56	PanCK	CK18	p16	HR-HPV	Pax-8	CD117	TTF-1	MLH1	PMS2	MSH2	MSH6
1	Pos (P)	Neg	--	Pos (F)	Pos (F)	Neg	--	Neg	Pos (F)	Neg	--	R	R	R
2	Neg	Pos (P)	--	--	--	--	--	--	--	--	--	--	--	--
3	Pos (P)	Pos (D)	Pos (D)	Pos (P)	Pos (D)	Pos (D)	Neg	Pos (D)	Neg	Neg	R	R	R	R
4	Neg	Neg	Pos (D)	Pos (D)	Pos (D)	Pos (P)	--	Pos (D)	Neg	Neg	LOST	LOST	R	R
5	Pos (D)	Neg	--	Pos (D)	Pos (D)	Pos (P)	--	Neg	Neg	Neg	LOST	LOST	--	R
6	Pos (D)	Pos (P)	--	--	--	--	--	--	--	--	--	--	--	--
7	Pos (D)	Pos (D)	--	Pos (D)	Pos (D)	Neg	--	Neg	Neg	Pos (F)	R	R	R	R
8	Pos (P)	Pos (P)	--	Pos (D)	Pos (D)	Pos (P)	--	Neg	Pos (P)	Neg	R	R	R	R
9	Pos (D)	Pos (P)	--	--	--	--	--	--	--	--	--	--	--	--
10	Pos (P)	Pos (P)	Pos (D)	Neg	Neg	Pos (D)	Neg	Neg	Neg	Neg	LOST	LOST	R	R
11	Neg	Pos (P)	--	--	--	--	--	--	--	--	--	--	--	--
12	Pos (P)	Neg	Pos (P)	Pos (P)	Pos (P)	Pos (D)	Neg	Pos (D)	Pos (D)	Neg	R	R	R	R
13	Pos (D)	Pos (D)	--	Pos (D)	Pos (D)	Pos (P)	--	Neg	Pos (F)	Neg	R	R	R	R
14	Pos (D)	Neg	Pos (D)	--	--	--	--	--	--	--	--	--	--	--
15	Pos (D)	Neg	--	Pos (P)	Pos (P)	Pos (P)	--	Pos (F)	Neg	Neg	R	R	R	R
16	Neg	Pos (D)	--	Pos (D)	Pos (D)	Pos (P)	--	Neg	Pos (F)	Neg	R	R	R	LOST
17	Pos (D)	Neg	Pos (F)	Pos (D)	Pos (D)	Pos (P)	--	Neg	Neg	Neg	R	R	LOST	LOST
18	Pos (P)	Pos (F)	Pos (D)	Pos (D)	Pos (D)	Pos (P)	--	Pos (P)	Neg	Neg	LOST	LOST	R	R
19	Pos (P)	Neg	--	--	--	--	--	--	--	--	--	--	--	--
20	Pos (F)	Pos (P)	Neg	Pos (D)	Pos (D)	Pos (P)	--	Neg	Neg	Neg	R	R	R	R
21	Pos (P)	Pos (P)	Pos (P)	Pos (D)	Pos (D)	Pos (P)	--	Neg	Neg	Neg	R	R	R	R
22	Pos (D)	Pos (D)	Pos (P)	Pos (F)	Pos (P)	Pos (D)	--	Neg	Neg	Neg	LOST	LOST	R	R
23	Pos (D)	Pos (D)	--	--	--	--	--	--	--	--	--	--	--	--
24	Pos (D)	Pos (D)	--	Pos (D)	Pos (D)	Pos (D)	Neg	Neg	Pos (P)	Neg	R	R	R	R
25	Pos (D)	Neg	--	Pos (P)	Pos (P)	Pos (D)	Neg	Pos (F)	Neg	Neg	LOST	LOST	R	R

Abbreviations: --, not performed; **Chg**, chromogranin; **D**, diffuse (50% labeling); **F**, focal (10% labeling); **HR**, high risk; **Neg**, negative; **P**, patchy (11–49% labeling); **Pos**, positive; **R**, retained nuclear staining; **Syn**, synaptophysin.