OPEN ACCESS – CASE REPORT

Mixed Small Cell and Large Cell Neuroendocrine Carcinoma involving the Endometrium: A Case Report and Literature Review*

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ABSTRACT

Neuroendocrine carcinoma (NEC) of the endometrium is a rare, aggressive subtype of endometrial cancer. We report a 61-year-old female with a history of breast cancer, s/p modified radical mastectomy, chemotherapy, radiotherapy and hormonal (tamoxifen) therapy, who presented with post-menopausal bleeding. Patient underwent TAH-BSO with lymph node dissection, and was diagnosed with a mixed small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC), confirmed by positive immunohistochemical staining for neuroendocrine markers. No other lesions were identified on PET-CT, making a primary endometrial NEC the most likely diagnosis. We review the clinical and pathologic characteristics of endometrial neuroendocrine carcinomas.

Key words: endometrial neoplasms, neuroendocrine carcinoma, large cell carcinoma, small cell carcinoma

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INTRODUCTION

Studies by the International Agency for Research on Cancer have shown that endometrial cancer is the 6th most commonly diagnosed cancer, the 2nd most commonly diagnosed female genital cancer, and the 14th leading cause of cancer death in women worldwide. In the past 10 years, the rates of endometrial cancer have increased in several countries, particularly in Japan, the Philippines, Belarus, Singapore, Costa Rica, and New Zealand. The Philippine Cancer Society estimates that in 2015, there were 2451 new cases of cancers of the corpus uteri and 565 deaths due to said cancer, however, the specific proportion by tumor type is not reported.[1-3]

While the majority of primary uterine corpus malignancies are endometrial endometrioid adenocarcinomas (80-90%), other significant tumor types include serous carcinoma (10%), clear cell carcinoma (<10%), undifferentiated carcinoma (≈2%), and neuroendocrine carcinoma (<0.8%), as well as carcinosarcomas and mesenchymal malignancies of the uterus (≈5%). Neuroendocrine tumors (NETs) of the gynecologic tract are uncommon, comprising about only 2% of gynecologic malignancies. Among gynecologic organs, neuroendocrine carcinomas (NECs) are most likely to occur in the uterine cervix, while they rarely occur in the uterine corpus. Primary endometrial neuroendocrine carcinoma is extremely rare, estimated to comprise less than 0.8% of endometrial carcinomas, with approximately a hundred cases reported in the literature.[1-7]

A search for reports in local literature revealed only a single published case of "poorly differentiated adenocarcinoma with neuroendocrine differentiation." At the study center, an average of approximately 330 hysterectomy specimens are received per annum, out of which approximately 60 are diagnosed with primary malignancy

of the endometrium. In descending order of frequency, these cases were diagnosed as endometrial endometrioid adenocarcinoma (89%), serous carcinoma (5%), carcinosarcomas and malignant mesenchymal tumors (3%), and clear cell carcinomas (2%). In comparison, over a five year period, only 2 resection specimens (≈0.6%), including the present case, were diagnosed as neuroendocrine carcinomas of the endometrium.[3]

Clinically, endometrial neuroendocrine carcinomas affect mainly perimenopausal or postmenopausal females. These tumors run an aggressive course with a propensity to metastasize. Histologically, they may present with morphology similar to small cell and large cell neuroendocrine carcinomas of the lung, and may also present in a mixed pattern with other forms of endometrial malignancy. Pathologic examination and immunohistochemical staining with neuroendocrine markers are essential for the proper diagnosis of these lesions.[4-6]

Here, we report a case of a 61-year-old female diagnosed with mixed small and large cell neuroendocrine carcinoma (NEC) of the endometrium. The clinicopathologic characteristics, management and outcomes of neuroendocrine carcinomas of the endometrium are reviewed.

CASE

A 61-year-old, nulligravid, Filipino female presented with postmenopausal vaginal bleeding beginning four months prior to referral to our institution. She had a previous history of breast cancer stage IIA, right, for which she underwent modified radical mastectomy ten (10) years prior to consult, followed by adjuvant chemotherapy and radiotherapy followed by adjuvant endocrine treatment with Tamoxifen for five (5) years. No evidence of disease metastasis or recurrence was noted on regular surveillance with mammography, bone scintigraphy and serum CA 15-3 monitoring. The patient also had a history of uterine myoma, status post myomectomy eighteen (18) years prior to consult, endometrial polyp, status post transcervical polypectomy seven (7) years prior to consult, and type II diabetes mellitus and hypertension.

Three months prior to referral, the patient consulted with a gynecologist. A transvaginal ultrasound revealed a thickened endometrium, and the patient underwent an endometrial biopsy, with a histopathologic diagnosis of endometrial endometrioid adenocarcinoma. She was advised total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO).

Physical examination on admission at our institution revealed no palpable abdominal mass or ascites. Internal examination showed a cervix that was firm, long and closed with no cervical motion tenderness and an anteverted uterus without palpable masses, enlargement or tenderness.

The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) with bilateral lymph node dissection and peritoneal fluid sampling with intraoperative findings of a slightly enlarged uterus, as well as adhesions between the left anterolateral aspect of the uterus and the posterior bladder wall which were lysed by sharp and blunt dissection.

On gross examination of the TAHBSO specimen at the pathology laboratory, the uterine corpus (5.5 x 5 x 4 cm.) was observed to have a 1.6 cm. thick anterior myometrium and a 2 cm. thick posterior myometrium, with a 5 x 2 cm. endometrial canal lined by 0.3 cm. thick endometrium. Sectioning revealed a 3 x 2.2 x 1.8 cm. cream tan, necrotic, friable, fungating endometrial mass arising in the posterior fundic area, with extension into the right anterior endometrium, and grossly infiltrating into the posterior myometrium. The mass was located about 2 cm. from the internal cervical os, and did not grossly extend to the lower uterine segment or cervix. The remaining myometrium demonstrated pink tan, whorled to trabeculated, rubbery cut surfaces. There was note of dense adhesions between the distal portion of the left fallopian tube (2.5 x 0.5 x 0.5 cm.) and left ovary (2.8 x 1.7 x 1 cm.), such that the fimbriae were not grossly distinguishable. Sectioning of the left ovary revealed cream tan to brown, smooth cut surfaces. Additionally, the right ovary (2.7 x 2.5 x 0.8 cm.) had a smooth outer surface and a 0.6 cm. unilocular cyst filled with mucoid material on sectioning. The right fallopian tube (5.5 x 0.5 x 0.5 cm.) was fimbriated and grossly unremarkable.

Microscopic examination of the endometrial mass disclosed an invasive tumor composed of large areas of malignant cells with interspersed areas of intratumoral necrosis and scant residual normal endometrial glands and stroma. The tumor demonstrated a mixed population of cells with approximately 60% composed of small cells with small hyperchromatic, ovoid to pleomorphic nuclei, nuclear molding and scant, poorly defined cytoplasm, arranged in solid sheets and nests. The remaining 40% was composed of larger cells with large, hyperchromatic to vesicular, ovoid to elongated to pleomorphic nuclei with nuclear molding, with scant to moderate cytoplasm, arranged in nests, glandlike and cribriform patterns and rosettes. The small cells also demonstrated crushing artifact (Figure 1).

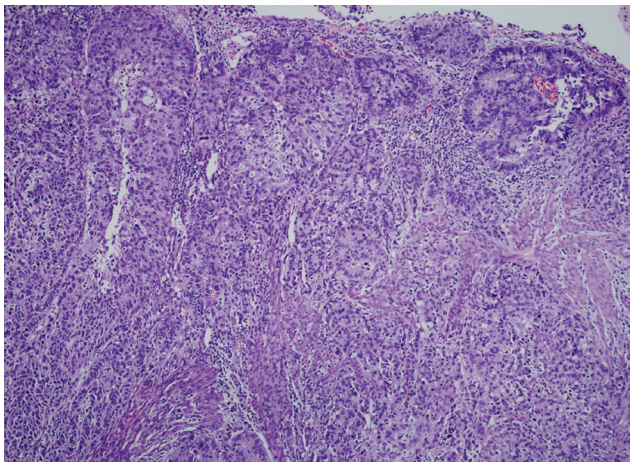

Figure 1. Low-power view of endometrial mass (H&E, 200x): Microsections reveal an infiltrative endometrial tumor composed of mixed small and large cells in nests, sheets, trabeculae, gland-like and rosette-like patterns.

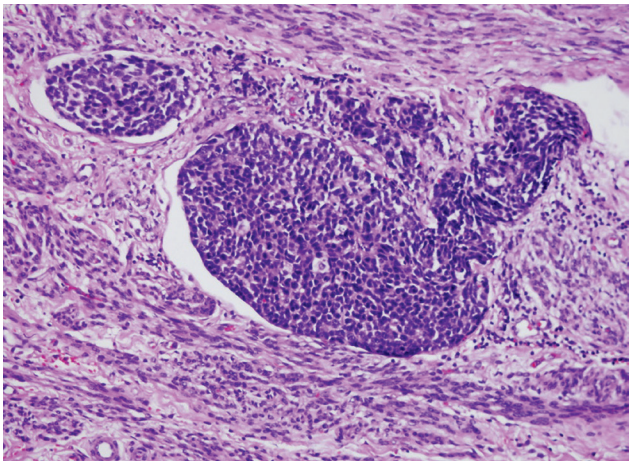

Figure 2. High-power view of infiltrating mass (H&E, 400x): Microsections of the myometrium demonstrate lymphovascular invasion by the small cell tumor component, with prominent nuclear crushing artifact.

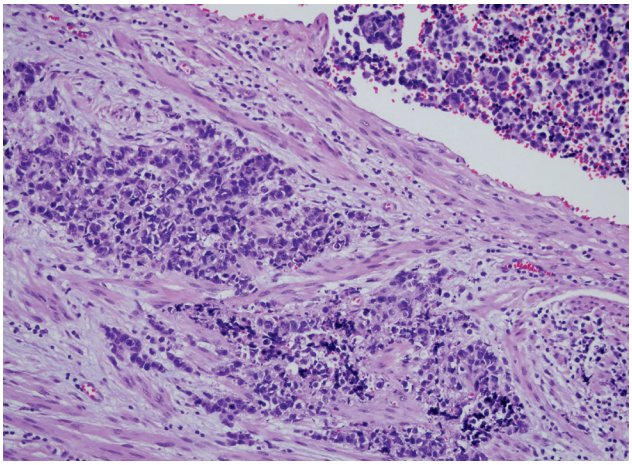

Figure 3. High-power view of infiltrating mass (H&E, 400x): Microsections of the myometrium demonstrate deep tumor infiltration (bottom) and extensive lymphovascular invasion (top) by the small cell tumor component, with prominent nuclear crushing artifact.

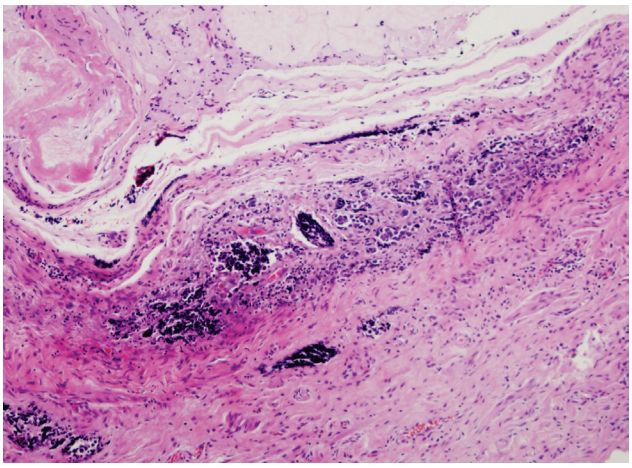

Figure 4. Low-power view of tumor in the adnexae (H&E, 100x): Microsections of the left ovary demonstrate nests of the small-cell tumor component present within the ovarian stroma and blood vessels (bottom), adjacent to a corpus albicans (top).

The tumor appeared to develop from within the endometrium, as the bulk of the tumor was located in the endometrial canal with invasion into the underlying myometrium. Microscopically, the invasion into the myometrium reached the subserosal area of the uterus, or more than 50% of the 2 cm thick myometrium. The tumor extended to the lower uterine segment but did not involve the cervix. The cervix showed benign endocervical and ectocervical epithelium with Nabothian cyst formation. There was also note of extensive lymphovascular invasion in the uterus, mainly of the small cell type (Figures 2 and 3). The left fallopian tube and ovary were also noted to have deposits of small cell type tumor cells, particularly within blood vessels (Figure 4). The right fallopian tube was unremarkable, and the right ovary was noted to have a mucinous cystadenoma. The parametria, right and left pelvic lymph nodes and peritoneal fluid were negative for tumor.

The initial impression was a poorly-differentiated endometrial carcinoma, to consider a high grade endometrioid carcinoma versus a dedifferentiated carcinoma versus a neuroendocrine carcinoma. Thus, immunohistochemistry was performed using the following stains to further characterize the tumor: CK (AE1/AE3), CD56 (CD564), Chromogranin (LK2H10), Synaptophysin (SP11), Pax8 (Biocare BC12) and WT-1 (6F-H2). The tumor cells showed diffuse positive staining for CK, CD56, Chromogranin and Synaptophysin, but were negative for Pax8 and WT-1 (Figure 5). Given the results, the tumor was diagnosed as a high grade neuroendocrine tumor with combined small cell and large cell histomorphology.

Given the presence of deep myometrial invasion and involvement of the left adnexa, the tumor was staged as pT3a by the AJCC 8th edition pathologic staging.

PET-CT scan performed three weeks after resection showed a prominent-sized hypermetabolic prebifurcation lymph node and normal-sized hypermetabolic mesenteric, para-aortic and left pelvic nodes which were suspicious for metastases. Thus, by FIGO 2015 staging the patient was considered as having a stage IIIC2 tumor. No other hypermetabolic areas were noted. Patient underwent adjuvant chemotherapy with six cycles of carboplatin and etoposide followed by radiotherapy to the pelvis (50 gy in 28 fractions) and paraaortic nodes (45 gy in 25 fractions). Treatment was generally well tolerated with few episodes of grade 1 thrombocytopenia. On reevaluation with PET-CT after eighteen months, no evidence of disease was noted and patient remained asymptomatic and stable.

DISCUSSION

Clinical Presentation

The 2020 WHO Classification of Tumors of Female Reproductive Organs divides primary neuroendocrine tumors of the female genital tract into low-grade neuroendocrine tumors (also known as carcinoid tumors) and high-grade neuroendocrine carcinomas (NEC), which includes small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinomas (LCNEC) of the endometrium. SCNEC and LCNEC of the endometrium

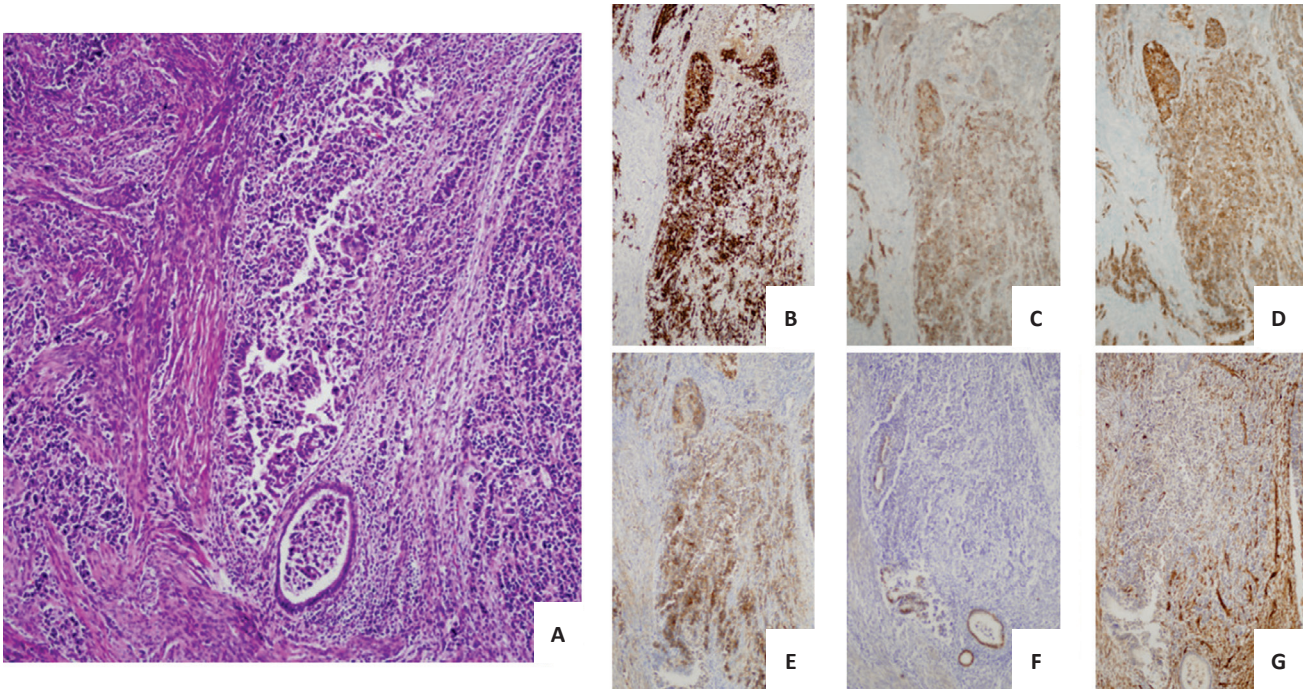

Figure 5. (A) Immunohistochemical Studies of Mass (H&E 100x) **(B)** Tumor cells are diffusely positive for staining with Cytokeratin; **(C)** Chromogranin; **(D)** Synaptophysin and **(E)** CD56; and **(F)** negative for staining with PAX8 and **(G)** WT-1.

** (F) Pax8 stains the residual atrophic endometrial glands but not the tumor cells while (G) WT-1 stains the smooth muscle of the myometrium but not the tumor cells.*

are very uncommon, estimated to comprise only 0.8% of endometrial carcinomas. Low-grade neuroendocrine tumors of the endometrium are even less common, with only three reported cases.[4-7]

Endometrial NECs usually occur in postmenopausal or perimenopausal patients, with an average age at diagnosis of 60 for SCNEC and 55 for LCNEC. It may be presumed that factors associated with increased risk for endometrial endometrioid adenocarcinomas such as nulliparity, increased BMI, diabetes mellitus, and certain endocrine therapies such as tamoxifen may also increase the risk of endometrial NECs, although this is not yet well studied due to the rarity of endometrial NECs. In the present case, the patient's risk factors include age, nulliparity, diabetes mellitus and history of breast cancer and tamoxifen therapy.[1,8]

Cortesi et al., reported that women with a history of breast cancer have a standardized incidence ratio (SIR) of 2.15 for development of endometrial cancer compared to the general population, with a higher SIR in patients who were treated with tamoxifen (2.5 compared to 1.34). The effect is bidirectional, with women with a history of endometrial cancer also having a higher risk of developing breast cancer (1.62). The effect of chemoradiotherapy for breast cancer on risk for endometrial cancer is not yet known, however, it has been observed that radiotherapy is associated with increased risk for second primary breast cancer, thyroid cancer and hematopoietic malignancies, and chemotherapy is associated with increased risk for hematopoietic malignancies.[8]

The most common clinical presentations of SCNEC and LCNEC are abnormal uterine bleeding and abdominal pain. Other reported presentations include abdominal enlargement, fatigue, and abnormal Pap smear findings. Paraneoplastic syndromes such as Cushing syndrome presenting as fatigue or visual impairment have also been reported.[4-7,9-14]

Histopathologic Characteristics

Grossly, endometrial NECs are often noted to be bulky, fungating masses, and deep infiltration into the myometrium is often noted. Some are described as polypoid or arising in a polyp, and may possibly have a more favorable prognosis according to a case series by Albores-Saavedra et al. Extra-uterine spread has been noted in several cases, including ovarian or tubal involvement, vaginal involvement, lymph node metastasis, and involvement of other pelvic and abdominal organs.[9-10]

Microscopically, SCNEC is composed of ovoid, poorly cohesive cells which may be arranged in solid, nested, trabecular, pseudoglandular or rosette-like patterns. The tumor cells have condensed chromatin and scant cytoplasm, with frequent nuclear molding, numerous mitotic figures, necrosis and apoptotic bodies, resembling small cell carcinoma of the lung. Similarly, LCNEC is characterized as having tumor cells arranged in solid, trabecular, nested, pseudoglandular and rosette-like patterns, trabeculae or cords, with peripheral palisading, and large, polygonal tumor cells with vesicular or hyperchromatic nuclei and prominent nucleoli. High mitotic activity and extensive geographic necrosis are also appreciated.[4-7,9-14]

To establish the diagnosis of NEC, a neuroendocrine growth pattern should be present in at least part of the tumor, together with expression of one or more neuroendocrine markers (Chromogranin, Synaptophysin

or CD56) in >10% of the tumor cells. However, it is important to note that 25-50% of typical endometrial adenocarcinomas may have minor populations of endocrine cells that are also positive for neuroendocrine markers. Neuroendocrine markers may also be detected in 30-40% of undifferentiated carcinomas, however, they exhibit focal staining of less than 10% of the total tumor cells. Histologically, NECs of the endometrium may appear as pure small cell or large cell neuroendocrine carcinomas, mixed small and large cell neuroendocrine carcinomas, or mixed with other histologic subtypes of endometrial tumors. The most common other cellular component in mixed tumors is endometrioid adenocarcinoma. Rare mixed tumors with serous cell carcinoma and clear cell carcinoma have also been reported.[4-7,9-14]

The histomorphologic differential diagnoses for SCNEC and LCNEC include high grade endometrioid adenocarcinoma, undifferentiated carcinoma, primitive neuroectodermal tumor, and carcinosarcoma. Thus, immunohistochemical staining is essential for properly identifying the neuroendocrine nature of the lesions. The majority of endometrial SCNEC and LCNEC are positive for synaptophysin, chromogranin A, CD56, neuron specific enolase and CD57. For SCNEC, synaptophysin is the most consistently expressed marker, while chromogranin is the most specific. These tumors also demonstrate high proliferative activity, with >50% of cells staining positive for Ki-67. SCNEC and LCNEC are usually positive for broad-spectrum cytokeratins such as CK AE1/AE3 and CAM5.2, and negative for CK20. Not unlike undifferentiated endometrial carcinomas, other markers of gynecologic origin such as PAX8, estrogen and progesterone receptor may or may not be positive. Generally, SCNEC and LCNEC are negative for mesenchymal markers such as desmin and S100. Based on these patterns of staining, it is reasonable to recommend that an initial immunohistochemical panel include neuroendocrine markers and epithelial markers when a neuroendocrine tumor is suspected.[4-7,9-14]

In addition to the morphology on H and E staining and positivity for neuroendocrine markers, van Hoeven, et al. proposed an additional criteria for diagnosis of primary neuroendocrine tumors of the endometrium: unequivocal evidence of endometrial origin in order to exclude the possibility of invasion or transfer of neuroendocrine tumors from other parts of the body, such as the cervix or lungs.[7]

In this case, the cervix was thoroughly sampled and showed no tumor involvement, ruling it out as the primary tumor site. Immunohistochemical staining for p16 and HR-HPV in-situ hybridization (ISH) are generally positive in primary cervical NECs, and may be useful in cases which are not as clear cut.[4,5]

The patient had a history of invasive breast carcinoma, raising the possibility of a metastatic breast tumor. Unfortunately, the full histopathology report was not available to the authors. Metastatic carcinoma from extragenital tumors to the female genital tract is uncommon, and most commonly affects the ovaries and vagina. A case series by Kumar and Hart (1982) reported that the primary extragenital tumors that most commonly metastasize to the uterine corpus are breast (42.9%), colon (17.5%), stomach (11.1%), pancreas (11.1%), gallbladder (4.8%) and lung (4.8%). Invasive lobular carcinoma is the most frequent histologic type of breast cancer to metastasize to the uterus, possibly due to loss of expression of the E-cadherin adhesion molecule enhancing spread. Metastases are most commonly distributed in the myometrium without involving the endometrium (63.5%), and rarely affect the endometrium without myometrial involvement.[15,16]

Stewart et al., have devised guidelines to aid in the distinction of endometrial and metastatic carcinomas. Careful consideration of tumor histomorphology is important, as metastatic tumors generally maintain an appearance resembling the tumor at the primary organ. Clues to a metastatic lesion include multifocal involvement, poor differentiation, lack of an identifiable precursor lesion, and a pattern of infiltration surrounding normal glands. In the patient's case, the lesion demonstrates spread from the main tumor mass in the posterior fundic area, and a progression from glandlike and cribriform patterns to solid sheets and nests, all of which diffusely stained positive for neuroendocrine markers, favoring a primary endometrial tumor (Figure 1). If needed, immunohistochemical staining with GCDFP, GATA-3 and CK7 may help uncover a breast primary, however these were not done in the patient's case due to budget constraints. The patient's follow-up in showed no breast tumor recurrence or second primary breast tumor, and postoperative PET-CT showed only hyperactivity of mesenteric, para-aortic and left pelvic nodes suspicious for metastases, with no other hyperactivity in other organs to suggest another primary tumor. Therefore, while a metastatic lesion cannot be completely ruled out, it is less likely.[15-17]

Pathogenesis

The pathogenesis of neuroendocrine tumors of the endometrium is not yet fully understood, however, immunohistochemical stains and molecular diagnostics provide a glimpse into the nature of the tumor. Mulvany, et al., report that some cases of endometrial NECs have been noted to have positive staining for p16, however, these did not show HR-HPV reactivity. This may indicate that unlike neuroendocrine tumors of the cervix, endometrial neuroendocrine tumors are not associated with high-risk HPV infection. However, the INK4a pathway may be involved through other means, causing expression of p16.[10,18]

Ariura, et al., report a case of combined LCNEC and endometrioid carcinoma, in which both tumor components were analyzed for mutation status, and were found to have identical alterations in the PTEN, PIK3CA and FGFR3 genes, although the endometrioid component contained an additional missense mutation in FGFR3. This suggests that the two components arose from a common precursor lesion. Additionally, it raises the possibility that some neuroendocrine tumors of the endometrium may be of the "Type I" or "CN Low" TCGA category of endometrial carcinoma, which is characterized by mutations in the PTEN, ARID1A and PIK3CA genes and history of estrogen exposure. This may be the pathway in patients with a history of tamoxifen intake, and is the most likely

pathophysiology in our patient. It should be noted that in addition to a history of 5 years of tamoxifen therapy, the patient also had a history of an endometrial polyp seven years prior, suggesting endometrial proliferation stimulated by the "pseudo-estrogen" effect of the hormonal therapy on the endometrium. Based on the patient's endometrial biopsy results three months prior to consult, it is possible that she developed an endometrial endometrioid adenocarcinoma, which later transformed into or was overtaken by the growth of the SCNEC and LCNEC components from a common precursor.[14,18]

Pocrnich, et al., in their study of 25 cases, report NECs with positive staining for p53 and intact MMR status. This suggests that the a population of neuroendocrine tumors of the endometrium may be of the "Type II" or "CN High" TCGA category of endometrial carcinoma, which is characterized by mutations in the TP53, PICK3CA, FBXW7, CHD4 and PPP2R1A genes. This is supported by findings of association with serous carcinoma and high grade endometrioid carcinoma, and noted propensity to spread.[6,18]

Prognosis and Management

SCNEC and LCNEC are described as having an unfavorable prognosis due to the early development of vascular invasion, lymph node and distant organ metastasis resulting in poorer survival outcomes compared to other histopathological subtypes of endometrial carcinoma. The majority of these tumors are diagnosed at advanced stages, and the outcome of the disease is predictably correlated to the stage at time of diagnosis. Overall, in previously reported cases, the outcome for NECs is poorer than that of similarly staged endometrioid carcinoma.[4-7,9-14]

Due to their rarity, at present, there is no defined regimen for the management endometrial neuroendocrine carcinoma. Surgical staging with debulking, chemotherapy and radiotherapy are among the treatment strategies available. Given its aggressive nature, surgical resection and multi-modal systemic therapy is warranted, and a multidisciplinary team is important. The most common chemotherapy regimens involved cisplatin and etoposide, similar to the treatment of small cell carcinoma of the lung. Other agents used include octreotide, doxorubicin and irinotecan. However, despite treatment, the prognosis is often poor.[4-7,9-13]

CONCLUSION

Neuroendocrine carcinoma of the endometrium is a rare but aggressive disease. Extrauterine spread and early development of distant metastasis is common. It is important for clinicians and pathologists to consider this disease entity when a poorly differentiated endometrial tumor is suspected, and perform the appropriate diagnostic procedures to guarantee proper identification and management of this malignancy. An initial immunohistochemical panel of neuroendocrine markers and epithelial markers are suggested when a neuroendocrine tumor is suspected. It is also important to rule out a neuroendocrine tumor with an origin outside of the endometrium. A multidisciplinary team approach is also important in the management of these cases. Due to its rarity and limited data available, more studies are needed to establish the optimal treatment for this malignancy.

ETHICAL CONSIDERATION

The case has been received and registered by St. Luke's Institutional Ethics Review Committee.

STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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