INTRODUCTION

Neuroendocrine carcinoma of gynecologic tract (gNET) is a very rare disease with a poor prognosis, accounting for 2% of all gynecologic cancers. GNETs are elusive and challenging to diagnose. Further, an unrecognized neuroendocrine component may lead to mismanagement and worse outcomes. Gynecologists should be familiar with presenting symptoms and diagnostic pitfalls. We performed a retrospective review of three gNET cases that presented at Richmond University Medical Center, Staten Island, NY, from May 2017 to August 2017. Three cases were identified. The major presenting symptoms were postmenopausal bleeding, heavy menstrual bleeding, bloating, and oliguria. All three patients underwent imaging, tissue sampling, and histologic subtyping. Etoposide and cisplatin were recommended for all three patients. Patient 1 committed suicide shortly after diagnosis. Patient 2 had advanced metastases and was not a surgical candidate; however, the patient did not receive the recommended imaging as per established guidelines. For Patient 3, immunohistochemical findings were suggestive of endometrial origin which is incredibly rare. Unfortunately, the neuroendocrine component was not identified until after radical hysterectomy was performed resulting in an inappropriate surgery. Due to gNET rarity, gynecologists may not have a strong index of suspicion for which to diagnose these tumors ultimately causing misdiagnoses and potential mismanagement. Gynecologists should be wary of diagnostic pitfalls.

Common clinical findings at initial presentation include abnormal vaginal bleeding and pelvic pain. The mean age of diagnosis is 61.4 years. The cervix is the most common location for neuroendocrine tumors of the gynecologic tract; however, they can also occur in the endometrium, ovary, fallopian tubes, vagina, and vulva. GNETs are an aggressive malignancy with early distant metastases and poor prognosis. Based on the Surveillance, Epidemiology, and End Results (SEER) database analysis done by Gibbs et al, extrauterine disease at the time of diagnosis was present in 66.9% of cervical NETs, 83.5% of ovarian NETs, and 83.6% of uterine NETs.

Histologic classification of gNET is derived from small cell carcinoma of the lungs. There are four categories of...
classification: typical carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma. Prognosis is largely based on histologic subtype. NECs often coexist with carcinoma in situ, invasive squamous cell carcinoma, or adenocarcinoma. When evaluating these tumors, it is important to identify the NEC component because it worsens the prognosis and will determine treatment.

Immunohistochemical markers drive the diagnosis of gNETs. For example, certain tumors, such as small cell NECs (SCNECs), display 33%-100% positivity for neuroendocrine markers. Chromogranin, synaptophysin, and CD56 are commonly used as neuroendocrine markers, although CD56 is relatively less specific to gNETs. Pax-8 and TTF-1 are other useful biomarkers for gNETS. Unfortunately, TTF-1 cannot be used to distinguish them from primary pulmonary tumors. Interestingly, unlike low-grade NECs, almost all high-grade cervical NECs are associated with HPV and stain positive for p16. Expression of p16 is used as a prognostic biomarker based on the fact that different types of cancer specific patterns of p16 expression. For example, patchy p16 is typical of endometrial origin, while strong/diffuse p16 is typical of cervical origin.

Though research on these tumors has been increasing, there has been no improvement in overall survival. Currently, treatment is modeled off of the guidelines for treating small cell carcinoma of the lung due to their histologic and genetic similarities. We report three cases that arose from the same institution and will discuss the limited current recommendations for treatment. Our unique contribution to the literature is the discussion of the diagnostic pitfalls discovered upon review of these cases. We hope that in reviewing diagnostic pitfalls that we may contribute to the literature to help improve patient management and outcomes.

The three cases of gNET were retrieved from the files of the Department of Gynecologic Oncology at the Richmond University Medical Center (RUMC), Staten Island, New York, between May 2017 and August 2017. We performed a retrospective review of these gNET cases. Data and imaging were extracted from the electronic medical record. Informed consent for publication was taken from the patient (Cases 2 and 3) or next of kin (Case 1).

2 | CASE REPORTS

2.1 | Case 1

A 73-year-old woman presented with postmenopausal bleeding, pelvic pain, bloating, and oliguria. Gross examination revealed a 16 weeks-sized uterus with a bulky cervix measuring 5 cm x 6 cm, and adnexa without palpable masses. Transvaginal ultrasound (TVUS) demonstrated a heterogeneous uterus with multiple fibroids and scant fluid in the endometrial cavity. A Pap smear done at that time was negative for intraepithelial lesions or malignancy. Endocervical curettage and endometrial biopsy were performed revealing scant superficial squamous cells and inactive endometrium. A CT of the abdomen and pelvis was performed, showing a heterogeneously enhancing soft tissue mass appearing to arise from the cervix and extending into the uterus (Figure 1). Extensive lymphadenopathy was noted.

Subsequently, multiple cervical biopsies were performed. Histologic examination of the tumor revealed a small round blue cell tumor with extensive necrosis, high mitotic rate, and individual cell apoptosis (Figure 2). The immunohistochemical stains were strongly and diffusely positive for Synaptophysin and p16, focally positive for chromogranin, and showed weak patchy positivity for CD10. The Ki-67 was 90%-95%. The morphologic and immunohistochemical features were consistent with high-grade small cell neuroendocrine carcinoma (SCNEC). The patient was discussed at our multidisciplinary treatment planning oncology conference. The planned treatment consisted of chemotherapy with cisplatin and etoposide. The patient was very distressed by her diagnosis and feared undergoing chemotherapy. Unfortunately, as per her family, the patient committed suicide by ingesting previously prescribed opioids prior to starting treatment.

2.2 | Case 2

A 44-year-old woman presented with a history of heavy menstrual periods, abdominal discomfort, and weight loss. On physical examination, she appeared cachectic and weak. Her abdominal examination was noticeable for distension and a mass in the right lower quadrant. An ultrasound
of the abdomen and pelvis showed an enlarged uterus (13.3 cm × 6.3 cm × 8 cm) with a markedly thickened endometrium (11 mm) containing complex material that distended the endometrial cavity to 30 mm. The patient was scheduled for a diagnostic laparoscopy and dilation and curettage. Due to the results of her preoperative laboratories including an elevated white blood cell count (WBC) of 36 000 (WBC/microliter), CEA of 15.9 ng/mL, and a CA-125 of 42 U/mL, her diagnostic laparoscopy was postponed and she was admitted for further evaluation.

A CT abdomen and pelvis revealed an enlarged uterus with markedly thickened heterogeneous endometrial and cervical canals (Figure 3A), multiple possible hepatic metastases (Figure 3B; largest: 5.1 cm × 4.9 cm), pulmonary nodules (Figure 4), and lytic osseous metastases located in the right pubis. An IR-guided biopsy of the largest liver nodule was performed. Similar to Case 1, the histologic findings were significant for a small round blue cell tumor with extensive necrosis and individual cell apoptosis (Figure 5). Pathology revealed positivity for pankeratin, CD56, synaptophysin, focal positivity for p53 and patchy positivity for p16. The Ki-67 was >90%. The patient was diagnosed with metastatic neuroendocrine carcinoma of gynecologic origin. Lung origin was considered less likely due to negative TTF-1. Due to the presence of metastatic disease, her tumor was staged as International Federation of Gynecology and Obstetrics (FIGO) IVB and she was determined to not be a surgical candidate. Recommendations of the multidisciplinary tumor board were for chemotherapy consisting of cisplatin and etoposide. She transferred care to a tertiary cancer center for a second opinion and was subsequently lost to follow-up.

2.3 | Case 3

A 77-year-old woman presented with heavy vaginal bleeding and abdominal pain. Physical examination was significant for a bulky uterus with a mass in the lower
TVUS revealed an enlarged uterus (10.6 cm × 7.3 cm), a right cystic mass adjacent to the uterus (7.2 cm) and a mural nodule (4.2 cm). A CT abdomen and pelvis with contrast showed a heterogeneously enhancing, lobulated mass. Next, a T2-weighted MRI of the abdomen and pelvis revealed a large, lobulated, heterogeneously enhancing mass (4.6 cm × 6 cm × 7.8 cm) arising within the cervix and extending superiorly obstructing the view of the endometrium. The mass was deemed highly suspicious for cervical carcinoma. It did not appear that the mass extended beyond the uterus and there was no noticeable pelvic or inguinal lymphadenopathy.

After discussion of the risks and benefits, the patient elected for a radical laparoscopic hysterectomy and bilateral salpingo-oophorectomy with pelvic lymph node dissection. Gross pathology revealed a bulky tumor (5.8 cm) involving the entirety of the lower uterine segment, upper endocervix and internal os and the right parametrium and fallopian tube. Histologic typing revealed a mixed cell carcinoma composed of both endometrioid adenocarcinoma (20%) and mixed small and large cell high-grade neuroendocrine carcinoma (80%; Figure 8). The neuroendocrine component of the malignancy was positive for PAX-8, synaptophysin, CD56, vimentin, and TTF-11. p53 and p16 staining showed wild-type expression. The adenocarcinoma component was negative for CEA but had patchy expression of p16 and vimentin. The Ki-67 index was 50%-60%. The morphologic and immunohistochemical findings were suggestive of endometrial origin. It was presumed that the tumor arose in the lower uterine segment close to the internal os and extended into the cervix, right parametrium, and right fallopian tube. She was staged as uterine carcinoma stage T3 N0.

The patient was discussed at our gynecologic tumor review board. She underwent adjuvant therapy with cisplatin and etoposide for six cycles, followed by 25 treatment fractions of high-dose rate intracavitary brachytherapy to the pelvis and three to the vaginal cuff. Since completion of brachytherapy, she had one episode of shortness of breath where she developed a pulmonary emboli. She was placed...
on anticoagulation medications, and chemotherapy was held. Two months after completion of brachytherapy, her pelvic examination was within normal limits, bimanual examination was negative for palpable masses, and pelvic sidewalls were free of lesions. The patient was doing well with no evidence of recurrence on examination. Unfortunately, she expired a year later (a total of 21 months after diagnosis), due to recurrence of distant lung metastases.

3 | DISCUSSION

We reported three cases of primary neuroendocrine tumors of the gynecologic tract including two cervical gynecologic NECs, “gNECs” (Cases 1 and 2), and a likely gNEC of uterine origin (Case 3). Neuroendocrine tumors represent a spectrum of malignancies arising from the neuroendocrine cell system. Similar to the patients presented in our case series, abnormal vaginal bleeding is the most common symptom at diagnosis. All three of our cases presented at an advanced stage at initial diagnosis with early nodal involvement, local extension, and metastases which is consistent with the literature showing that most gNETs have aggressive clinical courses.\(^1,5\) GNETs often coexist with carcinoma in situ, invasive squamous cell carcinoma, or adenocarcinoma.\(^1\) We discuss similarities regarding the workup and diagnosis for all three cases, and in addition, we comment on the pitfalls identified in diagnosis and management in the hopes to reveal learning opportunities for future physicians encountering gNETs.

Immunohistochemical markers drive diagnosis of gNETs.\(^1\) For each patient case, the immunohistochemical markers showed positivity for at least one neuroendocrine marker. Case 1 was positive for Chromogranin. Cases 1, 2, and 3 were positive for Synaptophysin. Case 2 and Case 3 were both positive for CD56. The expression of P16 is used as a prognostic biomarker for some types of cancer due to the fact that different cancer types have varied effects on p16 expression. Case 1 was strongly and diffusely positive for p16, Case 2 was focally positive, and Case 3 showed wild-type p16 expression with the adenocarcinoma component showing patchy expression. Patchy P16 is typical of endometrial origin, while strong/diffuse P16 is typical of cervical origin which helped differentiate cases 1 and 2 as cervical in origin versus case 3 as endometrial in origin.

The grading and classification of gNET was made in our cases according to biopsy and histologic subtype following the (now outdated) European Neuroendocrine Tumor Society (ENETS) criteria on grading adapted from guidelines for distant metastases.\(^6\) The Ki-67 for all three cases demonstrated grade 3 (G3): Case 1 was 90%-95% (G3), Case 2 was 90% (G3), and case 3 was 50%-60% (G3). This grading system has supplemented with the addition of the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system.\(^7\) The FIGO 2018 staging system, which incorporates CT imaging and pathologic findings, has improved staging of cervical NECs given the high propensity for lymphatic and hematogenous dissemination and is thus recommended.\(^7,8\)

Therapy is multimodal, even at an early stage. Options for FIGO Stage I-II disease are radical hysterectomy with pelvic lymph node dissection followed by adjuvant chemoradiation with concurrent cisplatin and etoposide.\(^9\) Locally advanced disease is treated by chemoradiation followed by additional
The most commonly reported needs include help with coping,mediate psychosocial support in order to best serve patients.

It is important to highlight that when giving a cancer diagnosis, attention should be made to provide patients with immediate psychosocial support. It is known in clinical medicine that patients who recently receive a cancer diagnosis have increased risk of suicide compared to cancer-free persons. During the past 20 years, there has been a rise in the therapeutic use, abuse, and nonmedical use of opioids, with hydrocodone becoming the leading prescribed medication in the United States. There is a concrete connection between prescribed average daily dose of opioids and opioid-related mortality. Therefore, providers should be mindful of the quantity of opioids they prescribe even when working with patients suffering from malignancies. Studies have also indicated that women are more likely to experience chronic pain and use prescription opioid pain medications for longer periods and in higher doses than men. This is an important implication to keep in mind for gynecologists as primary women's health providers.

In conclusion, we reported three cases of primary neuroendocrine tumors of the gynecologic tract (gNET). There is still much to be learned regarding the treatment and prognosis of gNETs. Areas of future research should include tracking response to proposed treatments so that these interventions may be adjusted appropriately and addressing the psychosocial components of cancer diagnosis. Finally, we should continue to report cases and the learning points that follow, so that data may be synthesized in a way to contribute to the small but growing body of literature on gNETs. Due to gNET rarity, gynecologists may not have a strong index of suspicion for which to diagnose these tumors ultimately causing misdiagnoses and potential mismanagement. Gynecologists should be wary of diagnostic pitfalls including late recognition of neuroendocrine components, inappropriate imaging, and inadequate psychosocial support following diagnosis.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
LEF: wrote manuscript, conducted background research, completed literature review, and edited manuscript drafts. RUG: involved in chart review, data collection, procured images, and edited manuscript drafts. NAL: gave original idea for project, involved in patient case identification, mentored every step of the project, and edited all drafts of paper.

CONSENT STATEMENT
Published with written consent of the patient.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author, LEF. The data are not publicly available due to patient privacy.
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