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ORIGINAL ARTICLE

Neuroendocrine Carcinoma of Female Genital Tract: Series of Nine Cases

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Abstract

Introduction Neuroendocrine carcinoma of female genital tract is a rare, aggressive disease, with incidence of less than 2%. Optimal therapy is poorly understood; hence, more case reports and studies are required to formulate appropriate therapy.

Methods Retrospective analysis by chart review of histopathology- and immunohistochemistry-confirmed neuroendocrine carcinoma between October 2014 and August 2019 in a tertiary care hospital.

Results Female genital tract neuroendocrine carcinoma was diagnosed in nine patients: Out of nine, six women were diagnosed with neuroendocrine carcinoma of the cervix, two with ovarian neuroendocrine carcinoma and one with neuroendocrine carcinoma of endometrium. Among the patients with neuroendocrine carcinoma cervix, vaginal bleeding and discharge were common and all were small-cell neuroendocrine carcinoma. Two of them were stage IIB and IIIC1r and received chemo-radiation and etoposide–platinum-based chemotherapy with progression-free survival of 53 months and 18 months, respectively. Four stage IVB patients received only chemotherapy and progressed or died few months after completion of treatment. Out of two with ovarian neuroendocrine carcinoma, one was small cell and another large cell. Large-cell case was in stage IIb, diagnosed postoperatively and lost to follow-up. Small-cell case was young and in stage IVB who progressed and succumbed after the second cycle of chemotherapy. One large-cell neuroendocrine carcinoma of endometrium stage IVB presented with extensive pelvic disease and skeletal and lung metastasis and defaulted after one cycle of chemotherapy.

Conclusions Neuroendocrine carcinoma patients, presented in advanced stage, are resistant to therapy and have an early demise. Although diagnosis is made, therapy has to be optimized by multicentric protocols.

Keywords Neuroendocrine carcinoma · Female genital tract · Systemic chemotherapy · Etoposide · Cisplatin

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Introduction

Neuroendocrine neoplasms (NENs) arise from the diffuse neuroendocrine cell system, commonly identified in the gastrointestinal tract, pancreas, lung and thymus. Gynecological NENs are uncommon with an incidence of less than 2%, either as primary or as secondary tumors [1, 2]. Endocrine cells are normal inhabitants of the para-urethral, Bartholin's and endocervical glands and of mesonephric rests from which NENs arise. The World Health Organization (WHO) updated the classification in 2014 and introduced changes to the terminology of neuroendocrine tumors [3, 4]. New terms adopted are low-grade neuroendocrine tumor (NET) and high-grade neuroendocrine

cancer (NEC). In the endometrium and cervix, high-grade neoplasms are much more prevalent than low grade, and among them occurrence in the cervix is common as compared to the corpus. In the ovary, low-grade tumors are more common than high-grade carcinomas, and the term carcinoid tumor is still used in WHO 2014.NECs have a high mitotic index, aggressive clinical course, propensity for extensive local invasion and distant metastases [5]. The prognosis and survival are poor regardless of stage at diagnosis and treatment given.

Histopathology and immunohistochemistry (IHC) are necessary for diagnosis. The diagnostic approach and FIGO staging of these tumors are similar to any other histological types of tumors arising from the cervix, uterus and adnexa.

There are limited data to guide management of NECs of female genital tract. Treatment options are often extrapolated from small-cell carcinoma of lung. The preferred treatment is a multimodal approach including surgery, chemo-radiation and systemic chemotherapy. The most common chemotherapy regimen used as initial therapy is a combination of cisplatin and etoposide [6, 7].

This study describes clinical presentation and evaluation and management of NECs of the female genital tract presented to the Department of Gynecologic Oncology, St. Johns Medical College, Bengaluru, from October 2014 to August 2019.

Materials and Methods

There were nine women diagnosed with NEC of genital tract from October 2014 to August 2019. All patients were followed up via telecommunication or outpatient visit. All patients were classified according to FIGO stage 2014 (FIGO 2018 for carcinoma cervix) and WHO 2014 classification. This study is approved by the ethics committee.

Results

The median age was 48 years (range 19–68) as depicted in Table 1. Out of nine, there were six women diagnosed with NEC of the cervix, two with ovarian NEC and one with NEC of endometrium.

NEC of Cervix (*N* = 6)

Among women with NEC of cervix ($N = 6$), four women had vaginal discharge and pain abdomen, three had irregular vaginal bleeding, two had post-coital bleeding and one had postmenopausal bleeding.

The staging of all women with NEC of cervix was determined according to the FIGO 2018. There were four women in stage IVB at presentation, while one each presented in stage II B and III C1(r) as depicted in Table 2.

Retroperitoneal lymph node metastasis was observed in five patients. Two women presented with visceral metastasis in lung and liver both. One woman had lung metastasis and one had liver metastasis. Histopathological type of tumor was small-cell neuroendocrine cancer (SCNEC) for all six women. Diagnosis of SCNEC was made on the basis of morphology and immunohistochemistry (IHC).

The combination regimen of etoposide and cisplatin was administered in four women (Table 3). In two women, cisplatin was replaced by carboplatin. Two women received concurrent chemo-radiation including external radiotherapy and vaginal brachytherapy with curative intent. Two patients received hemostatic radiation.

Two patients each with stage II B and III C1(r) are disease free at last follow-up with progression-free survival (PFS from date of diagnosis) of 53 months and 18 months, respectively. The average survival from date of diagnosis is 17 months (6–53 months). Patients with systemic disease either progressed or died few months after completion of treatment.

NEC of Ovary (*N* = 2)

One patient presented with irregular bleeding per vagina and pain abdomen. Imaging showed left adnexal solid–cystic mass. Her CA-125 was 357 U/ml. She was diagnosed as large-cell NEC (LCNEC) of ovary stage IIB postoperatively. She was lost to follow-up thereafter. Another patient was very young, aged 19 years, and presented with fever, loose stools and severe thigh pain. Her CA-125 value was 172 U/ml. PET-CT showed solid–cystic pelvic mass with peritoneal nodules, diffuse skeletal metastasis and bilateral pleural effusion. She progressed and succumbed after the second cycle of chemotherapy.

NEC of Endometrium (*N* = 1)

There was one woman with LCNEC of endometrium, presented with postmenopausal bleeding and pain abdomen. PET-CT showed extensive pelvic disease involving uterus (ovaries could not be identified separately), metabolically active pelvic and para-aortic lymph nodes, and skeletal and lung metastasis. Endometrial biopsy showed LCNEC. She defaulted after one cycle of chemotherapy due to financial constraints.

Table 1 The clinical presentation of nine patients with NEC

Site	Age (years)	Parity	Symptoms	Additional clinical findings
NEC cervix				
Case 1	20	Nulliparous	Irregular bleeding per vaginum	Adnexal mass
Case 2	35	Multiparous	Irregular bleeding + vaginal discharge + pain abdomen	No
Case 3	57	Multiparous	Postmenopausal bleeding	Palpable liver
Case 4	49	Primiparous	Irregular bleeding + vaginal discharge + pain abdomen	Abdominopelvic mass
Case 5	48	Multiparous	Post-coital bleeding + vaginal discharge + pain abdomen + loss of appetite + weight loss	No
Case 6	43	Multiparous	Post-coital bleeding + backache + vaginal discharge + pain abdomen	No
NEC ovary				
Case 7	50	Multiparous	Irregular bleeding + pain abdomen + loss of appetite	No
Case 8	19	Nulligravida	Fever + loose stools + thigh pain	No
NEC endometrium				
Case 9	68	Multiparous	Postmenopausal bleeding + pain abdomen	No

Discussion

Neuroendocrine tumors of the female genital tract are rare and contributed to 2% of all gynecological cancers. However, recently published studies showed an increasing incidence of these tumors, probably because of improvement in accuracy of diagnostic techniques such as advanced imaging and unique morphologic, ultrastructural and immunohistochemical features [5, 8].

NEC of Cervix

LCNEC and SCNEC comprise about 2% of cervical carcinomas and are highly aggressive, even at early stages [9]. Small-cell carcinoma accounts for 1–6% of cervical carcinomas. In this study, all NECs of cervix were SCNEC which is consistent with the literature [10].

The median age of presentation in this series was 45 years (range 20–57) which is very close to the median age reported by He and Cohen, respectively [11, 12]. In the present study, the most common presenting symptom was irregular bleeding which was similar to other studies [11]. In this study, four patients presented with systemic disease with liver and lung metastasis at the time of diagnosis. Out of six women, five women had retroperitoneal lymph node metastasis. Unlike our study, most of the women with small-cell carcinoma of cervix presented at early stage and only 49.5% had lymph node metastasis [12]. This disparity may be due to small number of cases in this study. However, 40–50% of SCNEC of genital tract exhibits lymph node metastasis at the early stage and presents with systemic disease involving the liver, lung, bone, brain, and even skin [13]. As all SCNEC behave aggressively, have a propensity to nodal and distant metastasis early and present in advanced stages at the time of diagnosis, computed tomography or PET-CT should be the choice of imaging to detect the extent of metastasis [14].

In this study, the PFS of stage II B and stage III C1(r) is 53 and 18 months, respectively. Both received chemotherapy etoposide and platinum and concurrent chemo-radiation. The average survival from the date of diagnosis is 17 months (6–53 months). In contrast, He et al. reported an average survival of 36.71 months (9–87 months) in 14 patients with NEC of cervix [11]. Another study by Viswanathan et al. also reported a median survival of 17 months (6–209) in 21 patients with SCNEC of cervix [15]. This may be because of small number of patients in our study, and four out of six patients had presented with systemic disease involving liver, lung or both. Stage at diagnosis is the most important factor to predict survival. It has been reported that the 5-year survival rates of patients with FIGO stage I–IIA, IIB–IVA and IVB SCNCC were 36.8%, 9.8% and 0%, respectively [12].

Table 2 The evaluation characteristics of nine patients with NEC

Site	Stage	PET-CT/CT*	HPR[+]	IHC[#]		
				Chr[$]	Syn[@]	CD56
NEC cervix						
Case 1	IV B	Huge cervical growth + bilateral adnexal masses + active pelvic nodes + lung metastasis	SC	–	Pos	Pos
Case 2	II B	Cervical growth + active bilateral pelvic lymph nodes	SC	Neg	Pos	Pos
Case 3	IV B	Cervical growth with pyometra + enlarged pelvic and para-aortic lymph nodes + lung and liver metastasis	SC	Pos	Pos	–
Case 4	IV B	Huge cervical growth + active pelvic and para-aortic lymph nodes + liver metastasis	SC	Pos	–	Pos
Case 5	IIIC1r	Cervical growth and active pelvic lymph nodes	SC	–	Pos	Pos
Case 6	IV B	Cervical growth with liver and lung metastasis	SC	Pos	Pos	–
NEC ovary						
Case 7	II B	Left adnexal mass	LC	Neg	Pos	Pos
Case 8	IV B	Solid–cystic pelvic mass with peritoneal nodules, uterus and cervix-normal + diffuse skeletal metastasis with bilateral pleural effusion	SC	Pos	Pos	Pos
NEC endometrium						
Case 9	IV B	Pelvic mass involving uterus and ovaries, cervix-normal + active pelvic and para-aortic lymph nodes + skeletal metastasis + lung metastasis	LC	–	Pos	Pos

*_PET-CT_ positron emission tomography–computed tomography

[+]_HPR_ histopathology report

[#]_IHC_ immunohistochemistry

[$]_Chr_ chromogranin A

[@]_Syn_ synaptophysin

NEC of Ovary

Primary NECs of ovary are very rare and aggressive tumors associated with other surface epithelial and germ cell neoplasms [16]. In the present study, there was one patient (age 50 years) of stage II B LCNEC of ovary, presented with irregular bleeding, pain abdomen and loss of appetite, which is similar to other studies [16–19]. Imaging showed left solid–cystic adnexal mass measuring 10 × 10 × 10 cms. Similarly, findings are mentioned in most of the case reports [17–19]. Most of the women present in early stage. They underwent ovarian cancer staging. Histopathology and IHC revealed pure LCNEC of ovary. In spite of presenting in early stage, the mean survival is less than 1 year [18].

Primary small-cell ovarian cancer is a highly aggressive tumor with an incidence rate of < 1% of all ovarian cancers and a poor outcome [20, 21]. Another patient in this study was very young, aged 19 years, diagnosed in stage IV B SCNEC ovary. SCNEC of ovary has been observed to occur in young age [22]. She presented with fever, loose stools and severe thigh pain. Her CA-125 value was 172 U/ml. PET-CT showed solid–cystic pelvic mass with peritoneal nodules, diffuse skeletal metastasis and bilateral pleural effusion. Young et al. reported clinicopathological details of 150 patients with SCNEC (hypercalcemia type). Most of the patients presented in stage I (50%). Only 1% of women were stage IV at diagnosis. Stage of the disease is the most important predictor of survival. Our patient was started with etoposide and cisplatin chemotherapy. However, she progressed and succumbed after the second cycle of chemotherapy. There was no clear-cut guideline for treatment due to paucity of data. Various chemotherapy regimens have been tried, such as etoposide, cisplatin, cyclophosphamide, vincristine, vinblastine and doxorubicin.

NEC of Endometrium

Primary NEC of endometrium is very rare, representing 0.8% of endometrial carcinoma, and includes both small-cell and large-cell variants [23]. LCNEC is less common than SCNEC of endometrium. Till date, around 21 cases of LCNEC endometrium are reported. 50–80% of NEC

Table 3 Details of management and outcome

Site	Surgery	Chemotherapy	Radiotherapy	OS[$] (duration)
NEC cervix				
Case 1	No	Etoposide + carboplatin × 2 cycles paclitaxel + carboplatin × 5 cycles	Hemostatic RT*	6 months
Case 2	No	Etoposide + cisplatin × 3 cycles f/b concurrent cisplatin	EBRT[@] and VBT[#]	53 months
Case 3	No	Etoposide + cisplatin × 6 cycles	No	6 months
Case 4	No	Etoposide + cisplatin × 3 cycles f/b paclitaxel + etoposide + cisplatin × 3 cycles	No	10 months
Case 5	No	Concurrent cisplatin f/b etoposide + carboplatin (AUC 5) × 3 cycles	EBRT + VBT	18 months
Case 6	No	Etoposide + cisplatin × 4 cycles then defaulted	Hemostatic	11 months (disease alive)
NEC ovary				
Case 7	TAH + BSO + ICO + RPLND[&]	–	–	Lost to follow-up
Case 8	No	Etoposide + cisplatin × 2 cycles	–	Progressed and died
NEC endometrium				
Case 9	No	Etoposide + cisplatin × 1 cycle	–	Defaulted

*_RT_ radiotherapy

[@]_EBRT_ external beam radiation therapy

[#]_VBT_ vaginal brachytherapy

[$]_OS_ overall survival

[&]_TAH + BSO + ICO + RPLND_ total abdominal hysterectomy + bilateral salpingo-oophorectomy + infracolic omentectomy + retroperitoneal lymph nodes dissection

endometrium is admixed with endometrioid adenocarcinoma FIGO grade 1 or 2. This study presents one woman with stage IV B LCNEC of endometrium.

She was 68 years old and presented with postmenopausal bleeding and pain abdomen. This is consistent with the literature which reports an average age of reported cases of LCNEC of 62.6 years and 75% of reported cases presented with abnormal or postmenopausal bleeding [24]. Six out of twenty-one reported cases in the literature presented in stage IVB [24].

There are limited data regarding treatment of LCNEC of endometrium. Treatment is largely extrapolated from NEC of lung. However, the preferred regimen is etoposide and cisplatin with an 83% recurrence-free survival reported at 3 years for LCNEC of the cervix [25]. Our patient received one cycle of chemotherapy and defaulted thereafter due to financial constraints.

Conclusions

NEC of female genital tract is a rare entity either primary or secondary. The most common is cervix, then ovary and very rarely endometrium. Most of the time presentation is similar to symptoms of respective general tumors.

They are very aggressive and mostly present in advanced stage with systemic disease. Comprehensive approach with multimodality treatment is the key for treatment. Because of limited data available, optimal therapy is poorly defined. Surgery is an option for early stage. Treatment with chemotherapy is the only option for patients with systemic disease. In spite of aggressive systemic chemotherapy, the survival is poor. To develop a better therapeutic strategy, multicenter prospective study is warranted. However, it is impractical due to rarity of NECs of female genital tract.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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