CASE SERIES

Rare genital system tumours, neuroendocrine neoplasms: case series and literature review

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Abstract

Neuroendocrine neoplasms (NENs) of the female genital tract are rare tumours. They behave more aggressively than other gynaecological cancers. Clinical presentation and treatment are not standard, and there is no specific guideline in place. Retrospective analysis of NENs of the female genital system was carried out between June 2020 and January 2024 in the tertiary care center Çam and Sakura City Hospital in İstanbul/ Turkey. Twenty patients who had neuroendocrine morphology in histopathology were included in the study. Fourteen were diagnosed as NENs, whereas six were diagnosed as neuroendocrine differentiated tumours. Most of the cases had poor prognosis, and average survival was 14±5.21 months, 35±18.54 months, and 34.25±7.57 months, respectively. Half of the patients relapsed with metastases. Like neuroendocrine carcinomas, neuroendocrine differentiated tumours also had poor prognosis. NENs are diseases with poor prognosis and are diagnosed at advanced stage. This depends on multifactorial effects. Molecular and genetic research may be helpful to optimise the management of this heterogeneous tumour group.

Keywords: Neuroendocrine neoplasm, Neuroendocrine differentiated tumour, Gynaecological neuroendocrine tumour.

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Introduction

Neuroendocrine neoplasms (NENs) are tumours that produce specific peptide and/or amine hormones and show neurological and endocrine differentiation. They express neuroendocrine markers, especially synaptophysin and chromogranin-A.[1] They are among the rarest cancers, both among all cancers and specifically among gynaecological cancers. NENs are most commonly seen in the gastrointestinal tract. In females, they account for less than 2% of all gynaecological cancers. Approximately half of the gynaecological NENs originate from the cervix; the vagina, vulva, and tuba are the rare sites of origin.[2] The prognosis is worse than that of the other types of female cancers, but data about their prognosis is limited. Today, the term "neuroendocrine neoplasm" is used for all types of neuroendocrine tumours. It includes, according to the World Health Organisation (WHO) fifth edition released in 2018,[3] low-grade neuroendocrine tumours (NETs) and high-grade neuroendocrine carcinomas (NECs).

This study aims to contribute to the literature by evaluating this heterogeneous tumour group's different clinical appearances.

Case Series

This retrospective study was conducted in the gynaecological oncology clinic of the tertiary care center Çam and Sakura City Hospital in İstanbul/Turkey. After approval from the institutional ethics review board, data of all patients who were diagnosed as having neuroendocrine tumour in the female genital system between June 2020 and January 2024 were retrieved from the archive records, and hospital operating system. Patients who were lost to follow-up and who were suspected of neuroendocrine tumours but could not be diagnosed with morphology/immunohistochemistry (IHC) staining were excluded. Cases were classified as NEC, NET, and mixed neuroendocrine and non-neuroendocrine neoplasm (MiNEN). Cases that had the morphological differentiation of neuroendocrine tumour cells but couldn't be confirmed as NENs by IHC staining were named tumours showing 'neuroendocrine differentiation'. Ages, tumour types, locations, and IHC staining characteristics of all patients were collected, and their treatment and prognosis were examined. Ethical approval was received from the hospital's Clinical Research Ethics Committee with decision number 27.12.2023-578. SPSS (version 23.0; SPSS Inc., Chicago, IL, USA) was used to evaluate statistical methods (descriptive statistics and survival analysis). Twenty patients with

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Table-1: Neuroendocrine classification and histopathology of the patients according to the origin of the tumour.

	Age	Tumour Location	Neuroendocrine Classification	FIGO Stage	Histopathological Features
CASE 1	71	Cervix	NEC	IV B	Non-small cell NEC
CASE 2	54	Cervix	NEC	III C2	Cervical NEC
CASE 3	89	Cervix	NEC	III C2	Large cell NEC
CASE 4	45	Cervix	NEC	III C1	Cervical NEC
CASE 5	58	Cervix	NEC	IV B	Cervical NEC
CASE 6	43	Cervix	MiNEN	I B2	Cervical adenocarcinoma and poorly differentiated NEC
CASE 7	63	Cervix	MiNEN	II B	Squamous cell carcinoma and poorly differentiated diffuse NEC
CASE 8	43	Cervix	Neuroendocrine differentiated tumour	III C2	Undifferentiated carcinoma
CASE 9	66	Cervix	Neuroendocrine differentiated tumour	III C1	Cervical adenocarcinoma and focal neuroendocrine differentiation
CASE 10	82	Endometrium	MiNEN	I B	Dedifferentiated carcinoma, Endometrioid carcinoma grade 1and neuroendocrine differentiated fields
CASE 11	74	Endometrium	MiNEN	III C1	Dedifferentiated carcinoma, Endometrioid carcinoma Grade 2 and neuroendocrine differentiated fields
CASE 12	68	Endometrium	MiNEN	I A	Endometrioid carcinoma Grade 1 and small cell/large cell NEC
CASE 13	83	Endometrium	Neuroendocrine differentiated tumour	II	Carcinosarcoma (serous carcinoma, poorly differentiated sarcoma) and neuroendocrine differentiated fields
CASE 14	72	Endometrium	Neuroendocrine differentiated tumour	III A	Squamous and neuroendocrine differentiated high-grade endometrioid carcinoma
CASE 15	57	Endometrium	Neuroendocrine differentiated tumour	I A	Squamous and neuroendocrine differentiated high-grade endometrioid carcinoma
CASE 16	62	Ovary	NEC	III A2	Small cell NEC
CASE 17	59	Ovary	MiNEN	III B	Serous ovarian carcinoma andsarcomatoid carcinoma, endometrial endometrioid carcinoma and large cell NEC
CASE 18	44	Ovary	Neuroendocrine differentiated tumour	III A2	Ovarian mucinous carcinoma (pancreas originated) and neuroendorine differentiated fields
CASE 19	28	Ovary	NET	I A	Ovarian NET Grade1 strumal carcinoid
CASE 20	47	Ovary	NET	I A	Ovarian NET Grade 1

(FIGO: International Federation of gynaecology and Obstetrics, NEC: Neuroendocrine carcinoma, MiNEN: Mixed neuroendocrine-non-neuroendocrine neoplasm, NET: Neuroendocrine tumour)

neuroendocrine morphology were included in the study. Fourteen cases were defined as neuroendocrine neoplasm; seven were in the cervix, three in the endometrium, and four in the ovary. Six cases were defined as neuroendocrine differentiated tumours (Table 1).

In the cervix, five NECs, two MiNENs, and two neuroendocrine differentiated tumours were noted. The average age was 59.11±15.17 years (range 43-89). The major complaint was vaginal bleeding. Patients were staged between IB and IVB, and the majority were at stage 3. Relapse occurred in three patients. The follow-up period was between one to 58 months, and the average survival was 14±5.21 months. The majority of the patients died within the first two years after diagnosis.

Table-2: Treatment, recurrence, and survival of the gynaecological NENs according to the tumour type.

	Tumour Type	Treatment	Adjuvant Therapy	Recurrence	Time to Recurrence(month)	Treatment for Recurrence	Follow-up Time (month)	Outcome
CASE 1	Cervical NEC	TAH BSO PPLND	CRT	X	-	-	10	Ex
CASE 2	Cervical NEC	TAH BSO PPLND	Chemotherapy	X	-	-	6	Ex
CASE 3	Cervical NEC	Treatment Refusal	X	X	-	-	1	Ex
CASE 4	Cervical NEC	PrimaryCRT	X	X	-	-	8	Alive
CASE 5	CervicalNEC	Primary CRT	X	+	11	Radiotherapy	14	Ex
CASE 6	CervicalMiNEN	Radical Hysterectomy BSO PPLND	CRT	+	15	CRT	58	Alive
CASE 7	Cervical MiNEN	Primary CRT	X	X	-	-	4	Ex
CASE 8	Cervical neuroendocrine differentiated tumour	Primary CRT	X	+	9	Wedge Resection MLND	15	Alive
CASE 9	Cervical neuroendocrine differentiated tumour	Primary CRT	X	X	-	-	21	Alive
CASE 10	Endometrial MiNEN	TAH BSO PPLND	Chemotherapy + Radiotherapy	X	-	-	35	Alive
CASE 11	Endometrial MiNEN	TAH BSO PPLND	Radiotherapy	+	12	CRT	12	Alive
CASE 12	Endometrial MiNEN	TLH BSO PPLND	Chemotherapy	X	-	-	7	Alive
CASE 13	Endometrial neuroendocrine differentiated tumour	TAH BSO(incomplete staging/medical reasons)	X(medical reasons)	X	-	-	23	Alive
CASE 14	Endometrial neuroendocrine differentiated tumour	TAH BSO PPLND	Chemotherapy	+	12	ChemotherapyExperimental drug	35	Ex
CASE 15	Endometrial neuroendocrine differentiated tumour	TLH BSO PPLND	Chemotherapy + Radiotherapy	+	2	Brain Radiotherapy	10	Ex
CASE 16	Ovarian NEC	TAH BSO PPLND	Chemotherapy	+	24	Chemotherapy	43	Alive
CASE 17	Ovarian MiNEN	TAH BSO PPLND	Chemotherapy	X	-	-	4	Alive
CASE 18	Ovarian neuroendocrine differentiated tumour	BSO	Chemotherapy	X	-	-	8	Ex
CASE 19	Ovarian NET	USO	X	X	-	-	40	Alive
CASE 20	Ovarian NET	USO	X	X	-	-	9	Alive

(NEN: Neuroendocrine neoplasm, NEC: Neuroendocrine carcinoma, TAH: Total Abdominal Hysterectomy, BSO: Bilateral Salpingooopherectomy, PPLND: Pelvic-paraaortic lymph node dissection, CRT: Chemoradiotherapy, MiNEN: Mixed neuroendocrine-non-neuroendocrine neoplasm, MLND: Mediastinal lymph node dissection, NET: Neuroendocrine tumour)

In the endometrium, three MiNENs and three neuroendocrine differentiated tumours were seen. The average age was 72.66±9.62 years (range 57-83). The major complaint was abnormal uterine bleeding and post-menopausal bleeding. Relapse occurred in two patients. The follow-up period was between seven and 35 months, and the average survival was 35±18.54 months.

In the ovary, two NETs, one NEC, one MiNEN, and one neuroendocrine differentiated tumour were seen. The average age was 48.0±13.54 years (range 28-62) years. The major complaint was abdominal swelling and non-specific abdominal pain. Relapse occurred in one patient. The follow-up period was between four and 43 months, and the average survival was 34.25±7.57 months (Table 2).

Discussion

Neuroendocrine carcinomas, which constitute 2% of all gynaecological malignancies, are rare malignant tumours. Their prevalence has increased recently, but this is thought to be related to the development of diagnostic methods rather than a real increase.[4] Histopathology and IHC staining are important in diagnosis. They should be used in combination because of different sensitivity and specificity.[1] Treatment is done by inferring from the body's other neuroendocrine tumours.[5] The prognosis is worse than those of the other cancers of the same tissue.

The first serious study on classification and nomenclature is the clinical document published by the Society of Gynaecology and Oncology (SGO) in 2011.[2,6] In 2018, the WHO simplified the classification by using the terminology of NEN, NET, and NEC.[3]

In the gynaecological tract, the most common site of NEN is the cervix.[4,7] Similarly, in the present study, the most common site was the cervix (50%), followed by the endometrium (21%) and the ovary (29%). While NECs are seen most commonly in the cervix, NETs are seen most frequently in the ovary.[2]

In the cervix, NECs have small- and large-cell variants. Small cells (80%) are more common than large cells (12%). NETs of the cervix are very rare in the literature. Twenty-five percent of all cases are mixed neoplasms.[8] All the seven cases of cervical NEN in the current study were high-grade NEC. No cervical NET was observed. MiNEN was observed in two cases (29%). While cervical NENs tend to occur at younger ages, ovarian and endometrial NENs are seen at later ages.[4] In the present study, however, patients with ovarian NENs were younger than those with cervical NEN. Most cervical NENs present in advanced stages, and lymphatic metastases are observed in approximately (40-50%).[9] In the present study, cervical NECs were at the advanced stage. Multiple metastases were observed in most of the patients, especially in the liver, and most of them died in the first two years. Two cases with mixed type were in the early stage. The one patient with SCC (squamous cell carcinoma) was treated with chemo-radiotherapy because of the 8 cm. tumour size and lived only four months. The one with adenocarcinoma had the longest survival with 58 months, although she had a poorly differentiated NEC and a metastasis in the femur. Neuroendocrine differentiated tumours had a better prognosis, although they presented at an advanced stage.

Endometrial NENs account for 0.8% of all endometrial cancers. Associations with other endometrial cancers are common. Therefore, these tumours may be incompletely described as poorly differentiated or dedifferentiated.[10] The mixed type is also common. Endometrial MiNENs can be seen as hyperplasia with atypia, endometrioid carcinoma, or neuroendocrine differentiation with carcinosarcoma.[8] All of the endometrial NENs in the current study were in the form of MiNEN and had a good prognosis. But the ones defined as 'neuroendocrine differentiation' had the worst prognosis than expected and had more metastatic lesions.

Ovarian NENs constitute 1-2% of all ovarian tumours. Ovarian NECs include small and large cells. Large-cell tumours are rare and aggressive.[2] The NET cases in this study were treated only surgically and had no recurrence. But the case with neuroendocrine differentiation had the worst prognosis because of the portal and coeliac invasion. The case with small-cell NEC had a good prognosis despite recurrence. The MiNEN with the large-cell type also had a second primary tumour in the endometrium and continued to progress despite receiving chemotherapy.

In the present study, it was noted that neuroendocrine differentiated tumours may have poor prognoses, as well as NECs. The weakness of the current study is that the study group did not consist of standard patients. This is because the cases had rare histopathologies. Since the disease prognosis is multifactorial, the clinical presentation of the patients and the treatments applied are not standard for each disease group. In addition, since there is no specific guideline for gynaecological NENs, the treatment is based on the treatment of other gynaecological tumours. The strength of this study is that the patient data is from each sub-gynaecological histopathological tumour group in the three most common gynaecological regions.

Conclusion

In conclusion, gynaecological system NENs are a rare tumour group. These tumours have poorer prognosis than non-neuroendocrine tumours of the same region. Neuroendocrine differentiated tumours which could not be defined as NECs may also have poor prognoses. It is very difficult to conduct a prospective study on this subject due to the low number of cases. For this reason, there are mostly case report studies in the literature. To reach more objective and general results on this subject, future studies at the molecular level are essential.

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AUTHOR'S CONTRIBUTION:

TC: Data acquisition, analysis, interpretation, final approval and agreement to be accountable for all aspects of the work.

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