Neuroendocrine Tumors of the Female Genital Tract

Ozlen Saglam and Ardeshir Hakam

Neuroendocrine tumors (NET) and tumors with focal neuroendocrine differentiation can arise throughout the female genital tract. NET can be pure or associated with various epithelial tumors such as ovarian mucinous, endometrioid, brenner and serous neoplasms, endometrial endometrioid adenocarcinoma, and endocervical adenocarcinomas [1–5]. Altogether these are rare entities, and pure NET does not comprise more than 2 % of female genital tract neoplasms [6]. The origin of neuroendocrine tumors was related to neural crest-derived amine precursor update and decarboxylation (APUD) cells until recent past. This concept was discarded mainly by LeDouarin' s work on chick-quail chimeras [7]. Current evidence is conclusive for endodermal origin of the gut and pancreatic neuroendocrine neoplasms [8]. Neuroendocrine cells have been identified within normal epithelium of the female genital tract [9]. These cells, as a part of diffuse neuroendocrine system, are likely to be the origin of neuroendocrine neoplasms other than tumors arising within teratomas.

Some NETs such as primary carcinoid tumors of the female genital tract share similar morphology to that of carcinoid tumors arising in other organ systems. It may be difficult to differentiate a primary disease from metastatic lesions in certain cases. There is no separate histologic grading system for NET arising in female genital tract. They are graded in a similar way to primary NET of the lung. NET can be functioning and produce hormones. Patients with these lesions may present with clinical syndromes as a result of ectopic hormone production. Here we discussed pathologic features and some of the clinical presentations of the female genital tract NET in specific anatomic sites.

O. Saglam, MD (✉) • A. Hakam, MD, MBA
Department of Pathology, Moffitt Cancer Center, Tampa, FL, USA
e-mail: ozlen.saglam@moffitt.org

A. Nasir, D. Coppola (eds.), *Neuroendocrine Tumors: Review of Pathology, Molecular and Therapeutic Advances*, DOI 10.1007/978-1-4939-3426-3_20

Ovaries

NETs arising in the ovaries are carcinoid tumors; small cell carcinoma hypercalcemic type; and small cell carcinoma pulmonary type. Primary ovarian large-cell neuroendocrine carcinoma has also been described in case reports [10]. Carcinoid tumors (well-differentiated neuroendocrine carcinoma) can be primary or metastatic from other anatomic sites. The morphologic subtypes include insular, trabecular, strumal, and mucinous carcinoids. They can also present with mixed morphologic features. Strumal and mucinous carcinoids contain epithelial elements which are thyroid tissue and mucinous epithelium, respectively. Primary ovarian insular and trabecular carcinoids are similar to intestinal counterparts. They can be observed in teratomas, mucinous tumors, and Sertoli-Leydig cell tumors [11]. Pure carcinoid tumors (strumal carcinoid) can be considered as monodermal teratomas. Most patients with carcinoid tumors are either postmenopausal or perimenopausal [12]. One-third of insular carcinoids are associated with carcinoid syndrome [13]. The rate of developing carcinoid syndrome was calculated around 8 % for the trabecular carcinoids in a study which used multiple tumor registries as a database [11].

Insular carcinoids are composed of solid nests of cells and small acini which may have eosinophilic secretions. Neoplastic cells have ample cytoplasm and centrally located round nuclei with finely stippled chromatin. The mitotic activity is low. Trabecular carcinoids are composed of one- to two-cell layered wavy ribbons and cords that are surrounded by fibromatous stroma (Fig. 1). Trabecular and mixed trabecular-insular carcinoids should be sampled thoroughly to rule out a strumal component. They are found in close proximity of thyroid tissue. Ultrastructurally, neurosecretory granules show variation in size and shape in the insular carcinoid

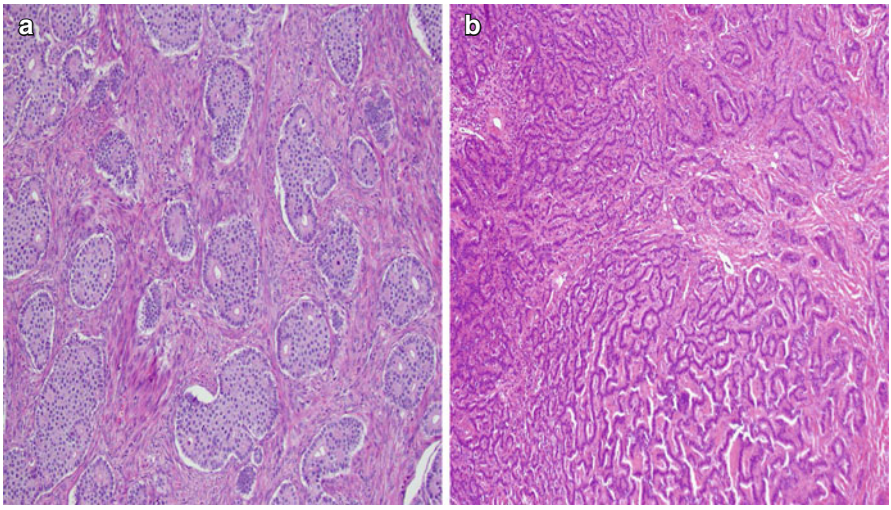

Fig. 1 Ovarian carcinoid tumors. (**a**) Insular pattern. (**b**) Trabecular pattern (10×)

tumors. On the other hand, relatively uniform and round secretory granules are observed in the trabecular type [14].

Mucinous carcinoids (goblet cell carcinoid) are rarely diagnosed in the ovary. A metastatic lesion should be ruled out before establishing the diagnosis of a primary ovarian neoplasm. Some morphologic features including presence of teratomatous elements or a surface epithelial tumor in combination, unilateral involvement of the ovaries, and absence of lymphovascular invasion are in favor of a primary neoplasm [15]. Mucinous carcinoid tumors are composed of numerous small glands and acini with small lumens. Neoplastic cells appear distended with intracytoplasmic mucin. There may be extracellular mucinous pools. Immunostains for chromogranin, CK20, and CK7 can be positive in mucinous carcinoids in varying percentages [16, 17].

Insular carcinoids are considered as potentially malignant tumors. In a series containing only insular, trabecular, and strumal subtypes, surgical treatment gave excellent results when the tumor was confined to the ovaries [12]. Mucinous carcinoids behave more aggressively than both insular and trabecular carcinoid tumors [18]. The degree of differentiation and presence of associated carcinoma are also related to overall prognosis [15]. Limited number of reported strumal carcinoid cases followed benign clinical course [19]. When a carcinoid tumor was part of cystic teratoma (Fig. 2), a significant difference was observed in multiple prognostic indicators compared to pure NET. The first group had smaller tumor size, lower rates of distant metastases, and hepatic involvement [11].

Metastatic carcinoid tumors almost always affect bilateral ovaries. They form well-circumscribed tumor nodules (Fig. 3), in contrast to single diffuse mass lesion of primary neoplasms. There is no definite morphologic feature or immunohistochemical panel that can differentiate primary versus metastatic carcinoid tumors of the ovary. Immunostain for CDX2 was proposed to use for discriminating primary disease from gastrointestinal metastasis [20]. There was weak staining in about 20 % of cases with CDX2 in this study. In another, diffuse CDX2 expression was reported in four out of six insular, one out of six strumal, and one out of one primary ovarian mucinous carcinoid tumors [21].

Small cell carcinoma of hypercalcemic type (SSC-H) is considered as undifferentiated carcinoma by some authors. These lesions are classified under miscellaneous category in the current World Health Organization's (WHO) book on classification of tumors of female reproductive organs [22]. They are highly aggressive tumors and commonly occur in young patients under 40 years of age. About two-thirds of cases are associated with elevated levels of calcium. They are usually unilateral fleshy white and solid lesions on gross examination. Diffuse small epithelial cells are separated by follicle-like spaces containing eosinophilic secretions. Brisk mitotic activity is observed throughout the lesion. Necrosis is also common. There are variants with large plasmacytoid/rhabdoid-appearing cells. They have glassy eosinophilic cytoplasm and nuclei with prominent nucleoli. Immunostains for WT-1, CD10, cytokeratins, and calretinin are useful in diagnosing SSC-H [23]. The staining pattern can be diffuse or focal with these markers. Recent whole-genome sequencing studies performed on SSC-H cases showed frequent inactivating germline and/or somatic

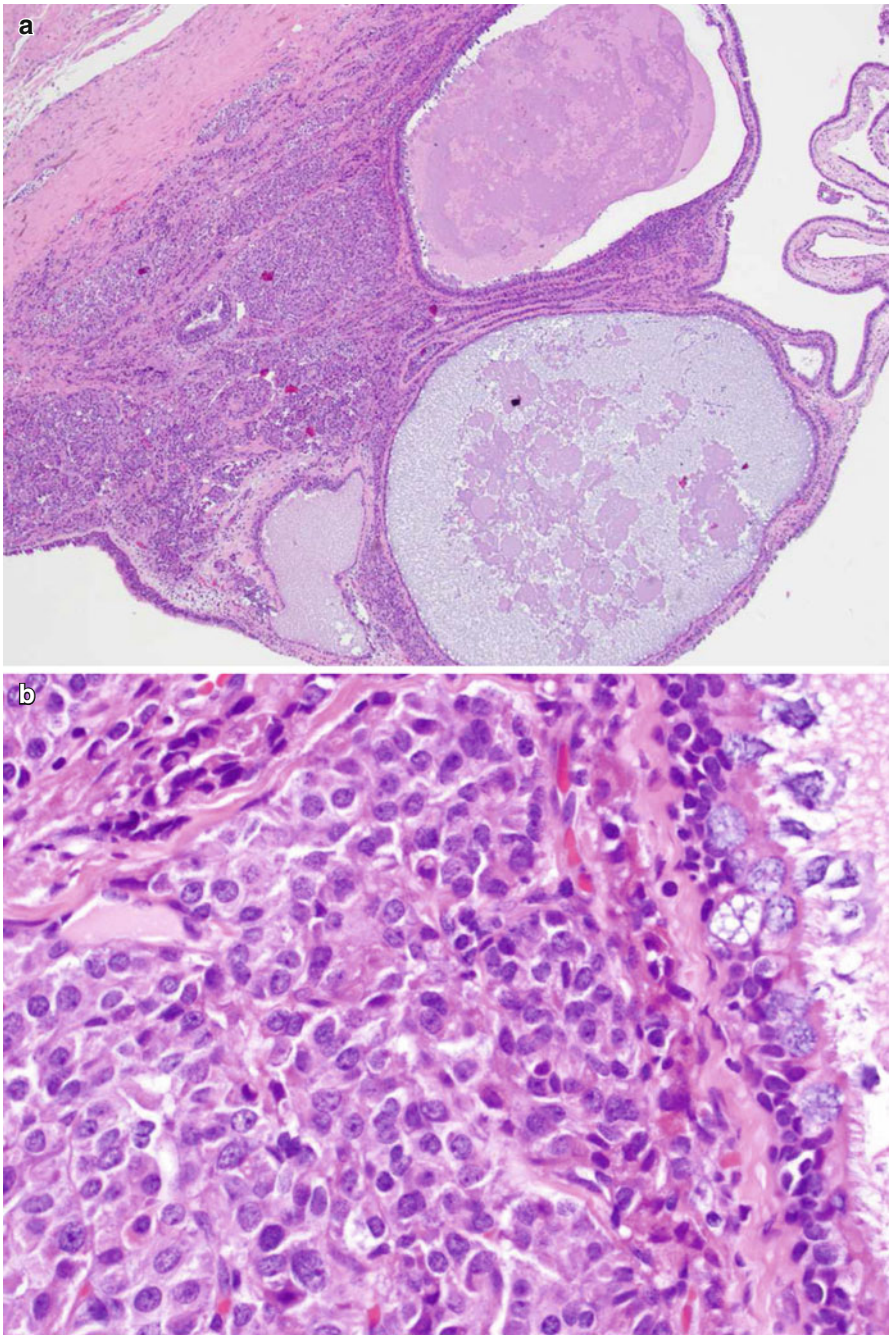

Fig. 2 (**a**) Incidental neuroendocrine tumor within a cystic teratoma (5×). (**b**) Neuroendocrine neoplasm and mucinous-type epithelium (20×)

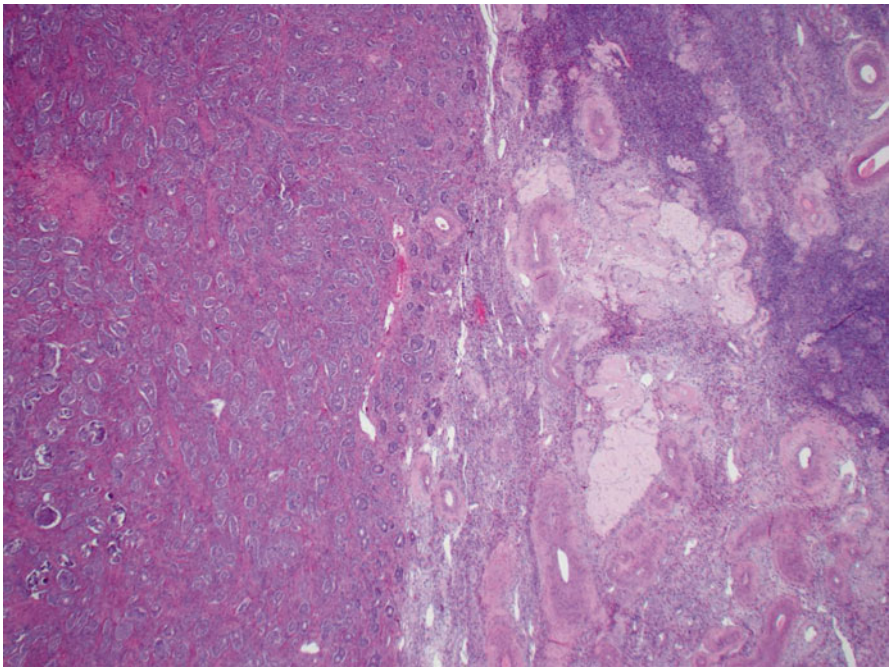

Fig. 3 Metastatic carcinoid tumor to the ovaries. Well-demarcated border between benign ovarian tissue and carcinoid tumor is characteristic for metastatic lesions (5×)

mutations in *SMARCA4* gene [24]. This mutation is also shared with malignant rhabdoid tumor arising in other anatomic sites. In addition to shared mutation, presence of some morphologic similarities brought the possibility of common cell origin for both neoplasms [25].

Small cell carcinoma of the ovary-pulmonary type (SSC-P) shows identical morphologic features to that of small cell carcinoma of the lung and can express TTF1 [4]. Clinical correlation is required before diagnosing a primary ovarian disease. They can be associated with other epithelial tumors such as endometrioid carcinoma, brenner tumor, and teratoma [26, 27]. Paraneoplastic syndromes are less common compared to primary lung disease. Cushing's syndrome and inappropriate secretion of antidiuretic hormone were described in the SSC-P type [28].

Fallopian Tube

Primary NET in the fallopian tubes is extremely rare. It was described in a postmenopausal woman with adnexal torsion [29].

Uterine Cervix

Cervical NETs were divided into low-grade and high-grade tumors in the current WHO's book on classifications of tumors of female reproductive organs [30]. Low-grade tumors are carcinoid and atypical carcinoid tumors. High-grade NETs of the uterine cervix are small-cell neuroendocrine carcinoma (SmCC) and large-cell neuroendocrine carcinoma. Low-grade NETs are extremely rare in the uterine cervix. Morphologic features of atypical carcinoid tumors include mild to moderate nuclear atypia, a mitotic count of 5–10 per high-power field (HPF), and focal necrosis [31]. High-risk human papillomavirus infection was detected in both low- and high-grade NETs of the cervix [32]. HPV 18 is more commonly identified compared to other subtypes. NET of the cervix can be diagnosed as mixed carcinoma with other epithelial tumors.

The mean age at diagnosis is 49 for endocrine tumors and 52 years for squamous cell carcinoma of the cervix [33]. Between 1977 and 2003, the mean annual incidence for SmCC of the uterine cervix was reported as 0.06 per 100,000 women. In comparison, the incidence of squamous cell carcinoma and adenocarcinoma was 6.6 and 1.2 per 100,000, respectively [34]. SmCC occurs most frequently in the cervix but can also involve the endometrium, ovary, fallopian tube, vagina, and vulva [35]. Majority of patients presents with vaginal bleeding [36]. There is a tendency for early hematogenous and lymphatic spread. Evaluation of the chest, abdomen, and pelvis by imaging studies is required as an initial diagnostic workup [37]. The morphology of SmCC is similar in all anatomic sites including the female genital tract. Tumor cells are composed of monotonous population of small cells with ovoid hyperchromatic nuclei and scant cytoplasm. Nuclear molding is frequently observed. There are abundant mitotic figures and apoptotic bodies. Prominent necrosis is also commonly seen. NET of the cervix can be associated with in situ and invasive endocervical adenocarcinoma and squamous cell carcinomas [38] (Fig. 4). One of the neuroendocrine markers such as synaptophysin, chromogranin, and CD56 is usually positive in NET of the cervix. However, negative results do not exclude the diagnosis of SmCC. By microsatellite analysis, loss of heterozygosity at several loci including 3p14, 5q31, 13q14, 17p13, 17q22, and 18q21 was detected in five out of ten SmCC components of mixed cervical cancers [39].

SmCC of the cervix is highly malignant tumor, and combination therapies are used in the treatment [40]. Patients with early-stage disease (I–II) showed significantly better survival rates compared with late-stage cancer (III–IV) in a small series [41]. A population-based study of Surveillance, Epidemiology, and End Results (SEER) reported worse prognosis in any kind of neuroendocrine tumors at all stages compared to squamous cell carcinoma of the cervix [33]. Patients with endocrine tumors presented at higher FIGO stage. The median survival for women with endocrine tumors was 22 months and for women with squamous cell carcinoma was 10 years.

High-grade neuroendocrine carcinomas of large cell type can have diffuse, organoid, trabecular, or cord-like patterns. Neoplastic cells have abundant cytoplasm, large nuclei, and prominent nuclei. The mitotic count is very high. Large-cell

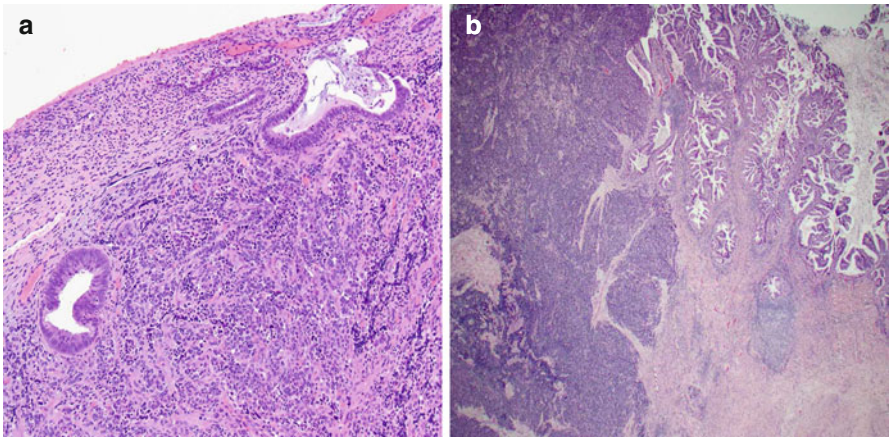

Fig. 4 Cervical NET. (**a**) Cervical adenocarcinoma in situ and NET (10×). (**b**) Invasive adenocarcinoma and NET (5×)

NET may also have glandular differentiation [42]. They are reactive with synaptophysin and chromogranin [43]. Microsatellite instability (MSI) was found in nine out of nine cases in a series. There were MSI and MMR defects. MSI-H was observed in around 89 % of cases. The latter was related to resistance to chemotherapy and radiation therapy [44]. By comparative genomic hybridization (CGH), amplification of 3q was the most remarkable chromosomal aberration detected in a case report [45].

Endometrium

NETs of the endometrium are usually observed in premenopausal and postmenopausal women [46]. They can present in combination with other common epithelial neoplasms. Small-cell NET, carcinoid, and large-cell NET were reported with papillary serous carcinoma of the endometrium [47–49]. The latter report describes epithelial pagetoid extension of neuroendocrine cells within benign and malignant endometrial glands. We observed similar phenomenon in the cervical and endometrial NET. Malignant tumor cells extended to benign endocervical and endometrial glands (Fig. 5). One can also assume that neoplastic cells are dropping down from the epithelium into the stroma rather than extending into it since their benign counterpart is present within the normal epithelium [9].

Large-cell neuroendocrine carcinoma was also observed in combination with grade 1 and 3 endometrioid adenocarcinoma [50]. A common tumor cell origin for epithelial and NET versus collision tumors is a proposed theory in the literature. Mhawech-Fauceglia et al. studied four mixed adenocarcinoma and high-grade neuroendocrine carcinomas arising from uterine corpus and the ovary by array CGH. Both components of all four cases showed almost similar genetic

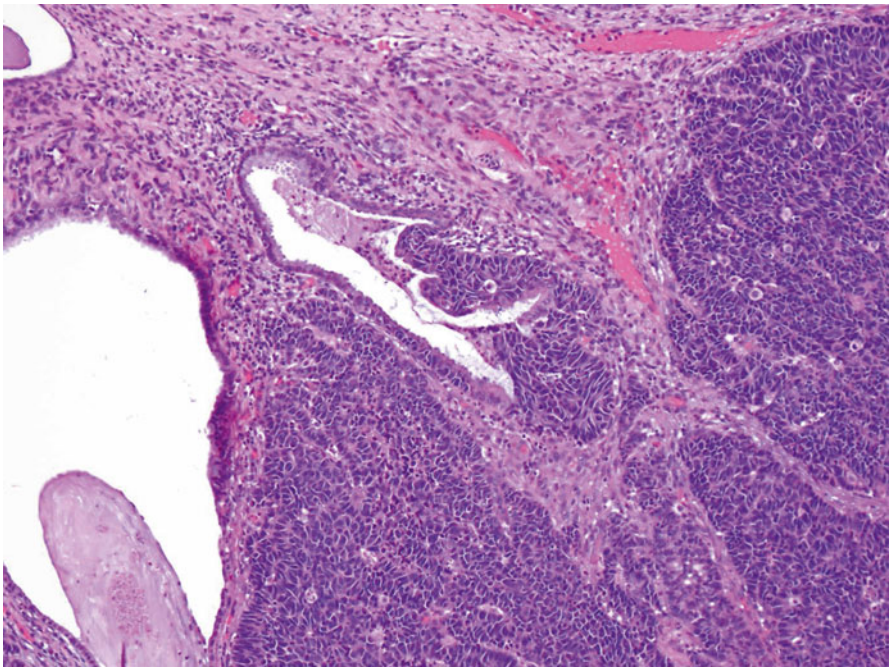

Fig. 5 Extension of NET to benign-appearing endometrial glands (10×)

abnormalities. In addition, NEC component demonstrated numerous additional genetic alterations including gain on 6p25.3-p21.2 and 19q12 and losses on 6q24.2-q27, 19q13.11-13.2, and 19q13.31-13.41 [51]. Their data indicate that high-grade neuroendocrine carcinoma and adenocarcinoma are genetically similar. However, neuroendocrine carcinoma component may be more dedifferentiated by acquiring more genetic abnormalities.

Taraif et al. reported neuroendocrine differentiation in 40 % of undifferentiated carcinoma of the endometrium. Most of these tumors had focal expression of neuroendocrine markers [52]. There was no survival difference in the group with neuroendocrine differentiation compared to the group without neuroendocrine features. This may be related to overall poor prognosis of undifferentiated carcinoma. Pure large-cell neuroendocrine and small-cell neuroendocrine carcinomas of the endometrium have a guarded prognosis [35, 53] (Fig. 6).

Vagina and Vulva

Primary small cell carcinoma and Merkel cell carcinoma (MCC) of the vagina are extremely rare [54, 55]. One of the small cell carcinoma cases occurred in a pregnant patient [56], and another was found in association with atypical vaginal

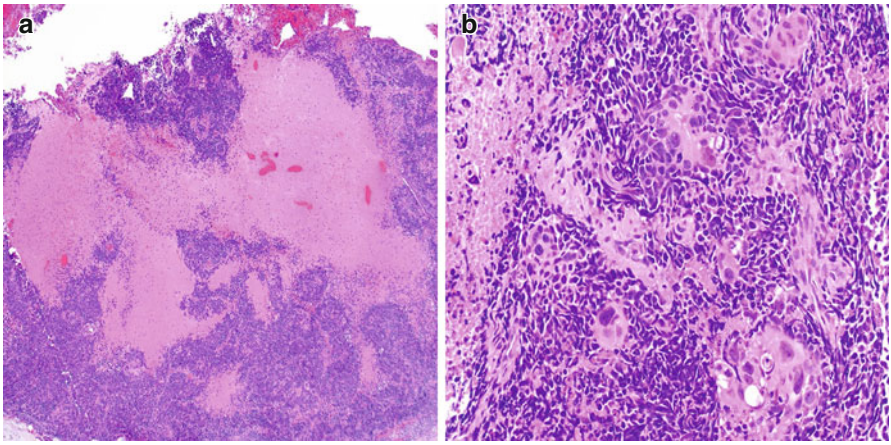

Fig. 6 Endometrial NET. (**a**) Areas of necrosis (5×). (**b**) Large cell features (10×)

adenosis [57]. Vaginal lesions should not be in continuity with the cervical tissue in order to rule out local extension of a cervical primary disease. There is no standard therapy for these aggressive tumors, and patients are treated in different combination of surgery, radiation, and chemotherapy [37].

Majority of neuroendocrine tumors of the vulva are MCC [37]. They have the same morphology and immunostaining profile with tumors arising in other anatomical sites. There is diffuse infiltration of dermis with uniform, small round cells with scant cytoplasm. Nuclei are pale and finely granular. Apoptotic bodies and mitotic figures are easily found. Characteristically cytokeratins highlight paranuclear cytoplasm in a dot-like pattern. Two out of 3778 MCCs occurred in the vulva in a population-based study [58]. Given the rarity of the lesion, it is difficult to estimate their behavior in this anatomic site. Primary clear cell carcinoid tumor of the vulva was also described [59]. These should be differentiated from other neoplasms with clear cell features such as malignant melanoma, metastatic renal cell carcinoma, and perivascular epithelioid cell tumor.

Conclusion

NET of the female genital tract is comprised of a spectrum of tumors with different clinical, prognostic, and pathologic features. It is important to differentiate primary and metastatic lesions since there is an overlap in the morphology of neuroendocrine tumors arising in different anatomical sites. Clinical and imaging correlation and appropriate amount of tissue sampling especially in mixed lesions are important for accurate diagnosis and clinical management of the disease.

Abbreviations

NET	Neuroendocrine tumors
SSC-H	Small cell carcinoma of hypercalcemic type
WHO	World Health Organization
SSC-P	Small cell carcinoma of the ovary-pulmonary type
SmCC	Small-cell neuroendocrine carcinoma
SEER	Surveillance, Epidemiology, and End Results
FIGO	International Federation of Gynecology and Obstetrics
MSI	Microsatellite instability
CGH	Comparative genomic hybridization
MCC	Merkel cell carcinoma

References

1. Roth LM, Goheen MP, Broshears JR. Malignant Brenner tumor of the ovary with transformation to trabecular carcinoid: an immunocytochemical and electron microscopic study. Int J Gynecol Pathol. 2012;31(1):91–7. PubMed Epub 2011/11/30. eng.
2. Ramalingam P, Malpica A, Deavers MT. Mixed endocervical adenocarcinoma and high-grade neuroendocrine carcinoma of the cervix with ovarian metastasis of the former component: a report of 2 cases. Int J Gynecol Pathol. 2012;31(5):490–6. PubMed Epub 2012/07/27. eng.
3. Chenevert J, Bessette P, Plante M, Tetu B, Dube V. Mixed ovarian large cell neuroendocrine carcinoma, mucinous adenocarcinoma, and teratoma: a report of two cases and review of the literature. Pathol Res Pract. 2009;205(9):657–61. PubMed Epub 2009/07/07. eng.
4. Grandjean M, Legrand L, Waterkeyn M, Baurain JF, Jadoul P, Donnez J, et al. Small cell carcinoma of pulmonary type inside a microinvasive mucinous cystadenocarcinoma of the ovary: a case report. Int J Gynecol Pathol. 2007;26(4):426–31. PubMed Epub 2007/09/22. eng.
5. Veras E, Deavers MT, Silva EG, Malpica A. Ovarian nonsmall cell neuroendocrine carcinoma: a clinicopathologic and immunohistochemical study of 11 cases. Am J Surg Pathol. 2007;31(5):774–82. PubMed Epub 2007/04/27. eng.
6. Rouzbahman M, Clarke B. Neuroendocrine tumors of the gynecologic tract: select topics. Semin Diagn Pathol. 2013;30(3):224–33. PubMed Epub 2013/10/23. eng.
7. Rosai J. The origin of neuroendocrine tumors and the neural crest saga. Modern Pathol. 2011;24 Suppl 2:S53–7. PubMed Epub 2011/04/06. eng.
8. Andrew A, Kramer B, Rawdon BB. The origin of gut and pancreatic neuroendocrine (APUD) cells – the last word? J Pathol. 1998;186(2):117–8. PubMed Epub 1999/01/30. eng.
9. Scully RE, Aguirre P, DeLellis RA. Argyrophilia, serotonin, and peptide hormones in the female genital tract and its tumors. Int J Gynecol Pathol. 1984;3(1):51–70. PubMed Epub 1984/01/01. eng.
10. Voutsadakis IA. Large cell neuroendocrine carcinoma of the ovary: a pathologic entity in search of clinical identity. World J Clin Oncol. 2014;5(2):36–8. PubMed Pubmed Central PMCID: PMC4014794, Epub 2014/05/16. eng.
11. Soga J, Osaka M, Yakuwa Y. Carcinoids of the ovary: an analysis of 329 reported cases. J Exp Clin Cancer Res. 2000;19(3):271–80. PubMed Epub 2001/01/06. eng.
12. Davis KP, Hartmann LK, Keeney GL, Shapiro H. Primary ovarian carcinoid tumors. Gynecol Oncol. 1996;61(2):259–65. PubMed Epub 1996/05/01. eng.
13. Robboy SJ, Scully RE, Norris HJ. Carcinoid metastatic to the ovary. A clinicopathologic analysis of 35 cases. Cancer. 1974;33(3):798–811. PubMed Epub 1974/03/01. eng.

14. Serratoni FT, Robboy SJ. Ultrastructure of primary and metastatic ovarian carcinoids: analysis of 11 cases. Cancer. 1975;36(1):157–60. PubMed Epub 1975/07/01. eng.
15. Baker PM, Oliva E, Young RH, Talerman A, Scully RE. Ovarian mucinous carcinoids including some with a carcinomatous component: a report of 17 cases. Am J Surg Pathol. 2001;25(5):557–68. PubMed Epub 2001/05/09. eng.
16. Vang R, Gown AM, Zhao C, Barry TS, Isacson C, Richardson MS, et al. Ovarian mucinous tumors associated with mature cystic teratomas: morphologic and immunohistochemical analysis identifies a subset of potential teratomatous origin that shares features of lower gastrointestinal tract mucinous tumors more commonly encountered as secondary tumors in the ovary. Am J Surg Pathol. 2007;31(6):854–69. PubMed Epub 2007/05/29. eng.
17. Jiang Y, Long H, Wang W, Liu H, Tang Y, Zhang X. Clinicopathological features and immunoexpression profiles of goblet cell carcinoid and typical carcinoid of the appendix. Pathol Oncol Res. 2011;17(1):127–32. PubMed Epub 2010/07/20. eng.
18. Talerman A. Carcinoid tumors of the ovary. J Cancer Res Clin Oncol. 1984;107(2):125–35. PubMed Epub 1984/01/01. eng.
19. Snyder RR, Tavassoli FA. Ovarian strumal carcinoid: immunohistochemical, ultrastructural, and clinicopathologic observations. Int J Gynecol Pathol. 1986;5(3):187–201. PubMed Epub 1986/01/01. eng.
20. Desouki MM, Lioyd J, Xu H, Cao D, Barner R, Zhao C. CDX2 may be a useful marker to distinguish primary ovarian carcinoid from gastrointestinal metastatic carcinoids to the ovary. Hum Pathol. 2013;44(11):2536–41. PubMed Epub 2013/09/14. eng.
21. Rabban JT, Lerwill MF, McCluggage WG, Grenert JP, Zaloudek CJ. Primary ovarian carcinoid tumors may express CDX-2: a potential pitfall in distinction from metastatic intestinal carcinoid tumors involving the ovary. Int J Gynecol Pathol. 2009;28(1):41–8. PubMed Epub 2008/12/03. eng.
22. Robert J, Kurman MLC, Simon Herrington C, Young RH. WHO classification of tumours of female reproductive organs. Lyon, France: WHO; 2014. p. 69–73.
23. McCluggage WG, Oliva E, Connolly LE, McBride HA, Young RH. An immunohistochemical analysis of ovarian small cell carcinoma of hypercalcemic type. Int J Gynecol Pathol. 2004;23(4):330–6. PubMed Epub 2004/09/24. eng.
24. Ramos P, Karnezis AN, Craig DW, Sekulic A, Russell ML, Hendricks WP, et al. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. Nat Genet. 2014;46(5):427–9. PubMed Epub 2014/03/25. eng.
25. Foulkes WD, Clarke BA, Hasselblatt M, Majewski J, Albrecht S, McCluggage WG. No small surprise – small cell carcinoma of the ovary, hypercalcaemic type, is a malignant rhabdoid tumour. J Pathol. 2014;233(3):209–14. PubMed Epub 2014/04/23. eng.
26. Eichhorn JH, Young RH, Scully RE. Primary ovarian small cell carcinoma of pulmonary type. A clinicopathologic, immunohistologic, and flow cytometric analysis of 11 cases. Am J Surg Pathol. 1992;16(10):926–38. PubMed Epub 1992/10/01. eng.
27. Fukunaga M, Endo Y, Miyazawa Y, Ushigome S. Small cell neuroendocrine carcinoma of the ovary. Virchows Arch. 1997;430(4):343–8. PubMed Epub 1997/04/01. eng.
28. Brown H, Lane M. Cushing's and malignant carcinoid syndromes from ovarian neoplasm. Arch Intern Med. 1965;115:490–4. PubMed Epub 1965/04/01. eng.
29. Crochet P, Luneau F, Rojat-Habib MC, Agostini A. Primary neuroendocrine carcinoma of the fallopian tube: a case report. Gynecol Oncol Case Rep. 2012;4:38–40. PubMed Pubmed Central PMCID: PMC3862233, Epub 2012/01/01. eng.
30. Robert J, Kurma MLC, Simon Herrington C, Young RH. WHO classification of tumours of female reproductive organs. WHO; 2014. p. 196–8.
31. Yasuoka T, Hashimoto H, Hamada K, Fujioka T, Nawa A. Atypical carcinoid of the uterine cervix with aggressive clinical behavior: a case report. Gynecol Oncol Case Rep. 2014;7:4–6. PubMed Pubmed Central PMCID: PMC3895285, Epub 2014/03/14. eng.
32. Mannion C, Park WS, Man YG, Zhuang Z, Albores-Saavedra J, Tavassoli FA. Endocrine tumors of the cervix: morphologic assessment, expression of human papillomavirus, and

evaluation for loss of heterozygosity on 1p,3p, 11q, and 17p. Cancer. 1998;83(7):1391–400. PubMed Epub 1998/10/08. eng.
33. McCusker ME, Cote TR, Clegg LX, Tavassoli FJ. Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma. Gynecol Oncol. 2003;88(3):333–9. PubMed Epub 2003/03/22. eng.
34. Chen J, Macdonald OK, Gaffney DK. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. Obstet Gynecol. 2008;111(6):1394–402. PubMed Epub 2008/06/03. eng.
35. Atienza-Amores M, Guerini-Rocco E, Soslow RA, Park KJ, Weigelt B. Small cell carcinoma of the gynecologic tract: a multifaceted spectrum of lesions. Gynecol Oncol. 2014;134(2): 410–8. PubMed Epub 2014/05/31. Eng.
36. Tsunoda S, Jobo T, Arai M, Imai M, Kanai T, Tamura T, et al. Small-cell carcinoma of the uterine cervix: a clinicopathologic study of 11 cases. Int J Gynecol Cancer. 2005;15(2): 295–300. PubMed Epub 2005/04/13. eng.
37. Crowder S, Tuller E. Small cell carcinoma of the female genital tract. Semin Oncol. 2007;34(1):57–63. PubMed Epub 2007/02/03. eng.
38. Abeler VM, Holm R, Nesland JM, Kjorstad KE. Small cell carcinoma of the cervix. A clinicopathologic study of 26 patients. Cancer. 1994;73(3):672–7. PubMed Epub 1994/02/01. eng.
39. Ishida GM, Kato N, Hayasaka T, Saito M, Kobayashi H, Katayama Y, et al. Small cell neuroendocrine carcinomas of the uterine cervix: a histological, immunohistochemical, and molecular genetic study. Int J Gynecol Pathol. 2004;23(4):366–72. PubMed Epub 2004/09/24. eng.
40. Dongol S, Tai Y, Shao Y, Jiang J, Kong B. A retrospective clinicopathological analysis of small-cell carcinoma of the uterine cervix. Mol Clin Oncol. 2014;2(1):71–5. PubMed Pubmed Central PMCID: PMC3915860, Epub 2014/03/22. Eng.
41. Wang Y, Mei K, Xiang MF, Li JM, Xie RM. Clinicopathological characteristics and outcome of patients with small cell neuroendocrine carcinoma of the uterine cervix: case series and literature review. Eur J Gynaecol Oncol. 2013;34(4):307–10. PubMed Epub 2013/09/12. eng.
42. Rhemtula H, Grayson W, van Iddekinge B, Tiltman A. Large-cell neuroendocrine carcinoma of the uterine cervix – a clinicopathological study of five cases. South African Med J. 2001;91(6):525–8. PubMed Epub 2001/07/18. eng.
43. Sato Y, Shimamoto T, Amada S, Asada Y, Hayashi T. Large cell neuroendocrine carcinoma of the uterine cervix: a clinicopathological study of six cases. Int J Gynecol Pathol. 2003; 22(3):226–30. PubMed Epub 2003/06/24. eng.
44. Mhawech-Fauceglia P, Chan A, Keitz B, Lele S, Cheney RT, Starostik P. Microsatellite instability in large cell neuroendocrine carcinoma of the female genital tract. Histopathology. 2009;55(5):621–5. PubMed Epub 2009/11/17. eng.
45. Kawauchi S, Okuda S, Morioka H, Iwasaki F, Fukuma F, Chochi Y, et al. Large cell neuroendocrine carcinoma of the uterine cervix with cytogenetic analysis by comparative genomic hybridization: a case study. Hum Pathol. 2005;36(10):1096–100. PubMed Epub 2005/10/18. eng.
46. Katahira A, Akahira J, Niikura H, Ito K, Moriya T, Matsuzawa S, et al. Small cell carcinoma of the endometrium: report of three cases and literature review. Int J Gynecol Cancer. 2004;14(5):1018–23. PubMed Epub 2004/09/14. eng.
47. Shaco-Levy R, Manor E, Piura B, Ariel I. An unusual composite endometrial tumor combining papillary serous carcinoma and small cell carcinoma. Am J Surg Pathol. 2004;28(8):1103–6. PubMed Epub 2004/07/15. eng.
48. Van Eeden S, Nederlof PM, Taal BG, Offerhaus GJ, Van Velthuysen ML. A tumour with a neuroendocrine and papillary serous component: two or a pair? J Clin Pathol. 2002;55(9): 710–4. PubMed Pubmed Central PMCID: PMC1769742, Epub 2002/08/27. eng.
49. Posligua L, Malpica A, Liu J, Brown J, Deavers MT. Combined large cell neuroendocrine carcinoma and papillary serous carcinoma of the endometrium with pagetoid spread. Arch Pathol Lab Med. 2008;132(11):1821–4. PubMed Epub 2008/11/04. eng.
50. Mulvany NJ, Allen DG. Combined large cell neuroendocrine and endometrioid carcinoma of the endometrium. Int J Gynecol Pathol. 2008;27(1):49–57. PubMed Epub 2007/12/25.eng.

51. Mhawech-Fauceglia P, Odunsi K, Dim D, Nowak N, Lele S, Cheney RT, et al. Array-comparative genomic hybridization analysis of primary endometrial and ovarian high-grade neuroendocrine carcinoma associated with adenocarcinoma: mystery resolved? Int J Gynecol Pathol. 2008;27(4):539–46. PubMed Epub 2008/08/30.eng.
52. Tafe LJ, Garg K, Chew I, Tornos C, Soslow RA. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently underrecognized neoplasms. Modern Pathol. 2010;23(6):781–9. PubMed Epub 2010/03/23. eng.
53. Nguyen ML, Han L, Minors AM, Bentley-Hibbert S, Pradhan TS, Pua TL, et al. Rare large cell neuroendocrine tumor of the endometrium: a case report and review of the literature. Int J Surg Case Rep. 2013;4(8):651–5. PubMed Pubmed Central PMCID: PMC3710906, Epub 2013/06/25. eng.
54. Tamura R, Yokoyama Y, Kobayashi A, Osawa Y, Shigeto T, Futagami M, et al. A case of small cell carcinoma of the vagina. Rare Tumors. 2013;5(4):e58. PubMed Pubmed Central PMCID: PMC3882930, Epub 2014/01/15. eng.
55. Coleman NM, Smith-Zagone MJ, Tanyi J, Anderson ML, Coleman RL, Dyson SW, et al. Primary neuroendocrine carcinoma of the vagina with Merkel cell carcinoma phenotype. Am J Surg Pathol. 2006;30(3):405–10. PubMed Epub 2006/03/16. eng.
56. ElNaggar AC, Patil AS, Singh K, Reed ME. Neuroendocrine carcinoma of the vagina in pregnancy. Obstet Gynecol. 2012;119(2 Pt 2):445–7. PubMed Epub 2012/01/25. eng.
57. Khurana A, Gupta G, Gupta M, Kaur M. Primary neuroendocrine carcinoma of the vagina with coexistent atypical vaginal adenosis: a rare entity. J Cancer Res Ther. 2013;9(2):328–30. PubMed Epub 2013/06/19. eng.
58. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol. 2010;37(1):20–7. PubMed Epub 2009/07/30. eng.
59. Srivastava SA, Wang Y, Vallone J, Felix JC. Primary clear cell carcinoid tumors of the vulva. Am J Surg Pathol. 2012;36(9):1371–5. PubMed Epub 2012/08/17. eng.