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GYNECOLOGIC CANCERS (NS REED, SECTION EDITOR)

Pathology of Neuroendocrine Tumours of the Female Genital Tract

Brooke E. Howitt[1] · **Paul Kelly**[2,3] · **W. Glenn McCluggage**[2,3]

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Abstract Neuroendocrine tumours are uncommon or rare at all sites in the female genital tract. The 2014 World Health Organisation (WHO) Classification of neuroendocrine tumours of the endometrium, cervix, vagina and vulva has been updated with adoption of the terms low-grade neuroendocrine tumour and high-grade neuroendocrine carcinoma. In the endometrium and cervix, high-grade neoplasms are much more prevalent than low-grade and are more common in the cervix than the corpus. In the ovary, low-grade tumours are more common than high-grade carcinomas and the term carcinoid tumour is still used in WHO 2014. The term ovarian small-cell carcinoma of pulmonary type is included in WHO 2014 for a tumour which in other organs is termed high small-cell neuroendocrine carcinoma. Neuroendocrine tumours at various sites within the female genital tract often occur in association with other neoplasms and more uncommonly in pure form.

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✉ W. Glenn McCluggage
glenn.mccluggage@belfasttrust.hscni.net

Brooke E. Howitt
bhowitt@partners.org

Paul Kelly
paul.kelly@belfasttrust.hscni.net

[1] Department of Pathology, Division of Women's and Perinatal Pathology, Brigham and Women's Hospital, Boston, MA 02115, USA

[2] Department of Pathology, Belfast Health and Social Care Trust, Belfast, UK

[3] Department of Pathology, Royal Group of Hospitals Trust, Grosvenor Road, Belfast BT12 6BA, UK

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Introduction and Background

Neuroendocrine tumours are uncommon or rare at all sites in the female genital tract. They are most common in the ovary where most are clinically benign carcinoid tumours arising in dermoid cysts. The uterine cervix is the most common site of high-grade neuroendocrine tumours in the female genital tract. The terminology has been confusing in the past, and to some extent currently, due to different nomenclatures being used at different sites. The updated 2014 World Health Organisation (WHO) Classification introduced changes to the terminology of neuroendocrine tumours at most, but unfortunately not all, sites in the female genital tract [1, 2]. Much of the change in terminology was to bring this broadly into line with that used for neuroendocrine tumours of the gastrointestinal tract, the most common site for these neoplasms. Table 1 lists the 2014 WHO categories of neuroendocrine neoplasms within the female genital tract.

In this review, neuroendocrine tumours are covered site by site within the female genital tract. Since the morphological appearances of high-grade neuroendocrine carcinomas are broadly similar at the various sites, the morphology of these is discussed in detail in the cervix section where these neoplasms are most common. Suggestions for changes to the WHO 2014 classification are also suggested to harmonise the terminology at all sites, and guidance is given as to which immunohistochemical markers are of value when the pathologist is faced with a disseminated neuroendocrine tumour of unknown origin. Given the recent adoption of a modification of the "gastrointestinal" classification for neuroendocrine

Table 1 World Health Organisation classification of neuroendocrine tumours of female reproductive organs

Site	Tumour category	Tumour type
Ovary	Monodermal teratoma and somatic-type tumours arising from a dermoid cyst	Carcinoid (subtypes of strumal and mucinous carcinoid)
	Miscellaneous tumours	Small-cell carcinoma, pulmonary type (small-cell carcinoma of neuroendocrine type)
	Miscellaneous tumours	Paraganglioma
Uterine corpus	Neuroendocrine tumours	Low-grade neuroendocrine tumour (carcinoid tumour)
	Neuroendocrine tumours	High-grade neuroendocrine carcinoma (small-cell and large-cell neuroendocrine carcinoma)
Uterine cervix	Neuroendocrine tumours	Low-grade neuroendocrine tumour (carcinoid, atypical carcinoid tumour)
	Neuroendocrine tumours	High-grade neuroendocrine carcinoma (small-cell neuroendocrine carcinoma, large-cell neuroendocrine carcinoma)
	Glandular tumours and precursors	Adenocarcinoma admixed with neuroendocrine carcinoma
Vagina	High-grade neuroendocrine carcinoma	Small-cell neuroendocrine carcinoma, large-cell neuroendocrine carcinoma
Vulva	Neuroendocrine tumours	High-grade neuroendocrine carcinoma (small-cell neuroendocrine carcinoma, large-cell neuroendocrine carcinoma), Merkel cell tumour

tumours at most sites within the female genital tract, the terminology of the former is first discussed together with the reasons for introducing this terminology in the gastrointestinal tract.

Terminology of Gastrointestinal Neuroendocrine Tumours

The term "carcinoid" is perhaps the most commonly recognised name applied to well-differentiated neuroendocrine tumours (WDNETs). It was originally coined in 1907 by Siegfried Oberndorfer to describe a distinct neoplasm in the small intestine composed of nests of uniform epithelioid cells [3]. Oberndorfer noted that these tumours, while bearing some resemblance to carcinomas, displayed much more indolent behaviour. His initial observations also concluded that the tumours were usually small, showed little tendency to infiltrate into the surrounding tissue and did not metastasise. While clearly some of these observations have now been shown to be invalid, the term carcinoid persists in several classification schemes and in the minds of many pathologists and clinicians.

There are several criticisms of the term carcinoid. Firstly, the term engenders an impression of benignity and belies the malignant potential of these tumours. Secondly, the broad term carcinoid fails to highlight the variability in the molecular biology and behaviour of these tumours depending on their site of origin, despite morphological similarity. Thirdly, merely applying the diagnosis of carcinoid provides limited prognostic information for the clinician and patient.

In 1963, Williams and Sandler proposed one of the most well-known classification systems for carcinoid tumours [4]. Their scheme categorised carcinoid tumours based on embryological origin as foregut (respiratory system, stomach, duodenum and proximal jejunum), midgut (distal jejunum, ileum, appendix and right colon) or hindgut (transverse and left colon and rectum) [4]. Implicit in this scheme is that tumours of similar embryological origin have a shared molecular biology. However, although plausible, it is now recognised that this is not biologically accurate, and moreover, it does not take account of the fact that these neoplasms occur at many other sites.

In 2000, a new approach to classifying gastrointestinal neuroendocrine tumours (GI-NETs) was introduced by the WHO, with a further modification in 2004 to incorporate pancreatic tumours [5]. Tumours were broadly separated into two groups according to morphology: well-differentiated neuroendocrine tumours (akin to classic carcinoids) and poorly differentiated tumours, which incorporated small-cell and large-cell neuroendocrine carcinomas. However, in this system, well-differentiated tumours (carcinoids) were further subdivided as benign, malignant or as having "uncertain" behaviour based on a combination of pathological features (vascular invasion, mitotic count, Ki67 proliferative index), staging criteria (size, nodal and distant metastases) and clinical features such as functional hormone production [6]. Moreover, so-called carcinoids demonstrating clearly malignant behaviour were termed "well-differentiated neuroendocrine carcinomas," despite being morphologically identical to clinically benign tumours. This system also provided site-specific criteria for classifying tumours at various sites in the gastrointestinal tract thereby recognising the biological variability of these neoplasms. The approach offered by this scheme was broadly accepted in most European institutions but found less favour in the USA [7]. Ultimately, it had several important limitations. Firstly, as a hybrid system requiring a combination of morphological, grading and staging parameters to classify and define the tumour, it was impractical and could only be fully applied to resection specimens, where all of the features could be assessed. Furthermore, at some sites, for example the

pancreas, up to 5% of tumours classified as benign were found to metastasise, and in some series, 40% of the uncertain category of WDNETs recurred or metastasised [7, 8]. Finally, from a clinical perspective, the use of an uncertain category is suboptimal, if not unhelpful, particularly with regard to providing explanations to patients about their disease, treatment and prognosis.

In 2010, the WHO introduced a revised scheme [9]. The first major deviation from its predecessor was an assumption that all GI-NETs had malignant potential. The revision retained the importance of morphological assessment of tumour differentiation but utilised a formal grading system based on proliferative activity (using both mitotic count and Ki67 staining) and, for the first time, introduced a formal site-specific TNM staging system [9–11]. Importantly, as the grading and staging parameters are independently assessed, it meant that the classification could be applied to small biopsies, as well as resection specimens. The nomenclature adopted in this scheme is much simpler than the earlier 2000/2004 systems; well-differentiated tumours are classified as NET grade 1 or 2 and poorly differentiated tumours as neuroendocrine carcinoma (NEC), grade 3. The assumption is that morphology and grade correlate such that well-differentiated tumours (grade 1 or 2) have a low proliferative index and vice versa for poorly differentiated tumours (grade 3).

Neuroendocrine Tumours of Ovary

General Comments

In the 2014 WHO Classification of ovarian tumours, there is no separate category of neuroendocrine neoplasms, unlike at other sites in the female genital tract [1]. This is a shortcoming of the 2014 Classification. In the following sections, the various neuroendocrine tumours of the ovary are discussed.

Carcinoid Tumours of Ovary

In the 2014 WHO Classification of ovarian neoplasms, the term carcinoid tumour is still used and this is included in the category of "Monodermal teratomas and somatic-type tumours arising from a dermoid cyst" [1]. Although the term carcinoid tumour is still used, well-differentiated neuroendocrine tumour, grade 1 is listed as a synonym. Ovarian carcinoid tumours are the most common primary neuroendocrine neoplasm in the female genital tract, and almost all arise within teratomas, especially dermoid cysts (mature cystic teratomas) reflecting their WHO Classification. However, microscopic foci of carcinoid tumour are rarely identified in other ovarian neoplasms, for example, germ cell tumours other than dermoid cyst, such as yolk sac tumour, Brenner tumour and Sertoli-Leydig cell tumour. It is uncommon for patients with primary ovarian carcinoids to have the carcinoid syndrome, although this occasionally occurs even in the absence of metastatic disease.

Most primary ovarian carcinoids are unilateral, small and incidental microscopic findings in a dermoid cyst, although when larger they may be visible grossly, usually in the form of a yellow nodule. Morphologically, there are four main variants of primary ovarian carcinoid tumour; these comprise insular (the most common), trabecular, strumal and mucinous (goblet cell) with the latter two listed as variants of carcinoid tumour in WHO 2014 [1, 12].

Insular carcinoids are morphologically identical to midgut carcinoids and are composed of nested/insular arrangements, sometimes with small acinar or tubular formations [13]. The tumour cells are polygonal with round or ovoid nuclei with a so-called "salt and pepper" chromatin and abundant cytoplasm. Eosinophilic cytoplasmic granules may be seen. There is usually little in the way of nuclear atypia, and mitotic activity is low. The tumour cells are often set in a conspicuous stroma with a rather hyaline appearance, occasionally with psammomatous calcification.

Trabecular carcinoids are less common than insular and are composed of parallel trabecular/wavy ribboned arrangements of regular cells with similar nuclear features to those seen in insular carcinoids and set within a fibrous stroma [14, 15]; they are morphologically similar to hindgut carcinoids. Strumal carcinoids are composed of an admixture of carcinoid elements (usually either insular or trabecular in type with the latter more common) and thyroid tissue [16]. The two elements may be spatially separate or intimately admixed. Intestinal-type mucinous glands are often present (40% of cases). Mucinous (goblet cell) carcinoid is the rarest primary ovarian carcinoid tumour and is composed of small glands or acini lined by columnar or cuboidal epithelium with abundant intracytoplasmic mucin and variable numbers of goblet cells [17].

Figure 1 illustrates the four types of primary ovarian carcinoid tumour.

Immunohistochemistry of Ovarian Carcinoid Tumours

Most ovarian carcinoid tumours of insular type are diffusely positive with the neuroendocrine markers chromogranin, synaptophysin and CD56. Trabecular carcinoids are also usually positive with these markers, although a pitfall is that they may be chromogranin negative; this reflects the fact that they are analogous to hindgut carcinoids which are often chromogranin negative. This can result in confusion with a Sertoli cell tumour which can also have a trabecular architecture. The latter are usually positive with inhibin and calretinin and negative with synaptophysin, while trabecular carcinoids exhibit the converse immunophenotype. Insular and mucinous carcinoids are often positive with CDX2 [18]. Both insular and trabecular carcinoids are typically CK7 positive and CK20 negative [18]. In contrast, mucinous carcinoids are

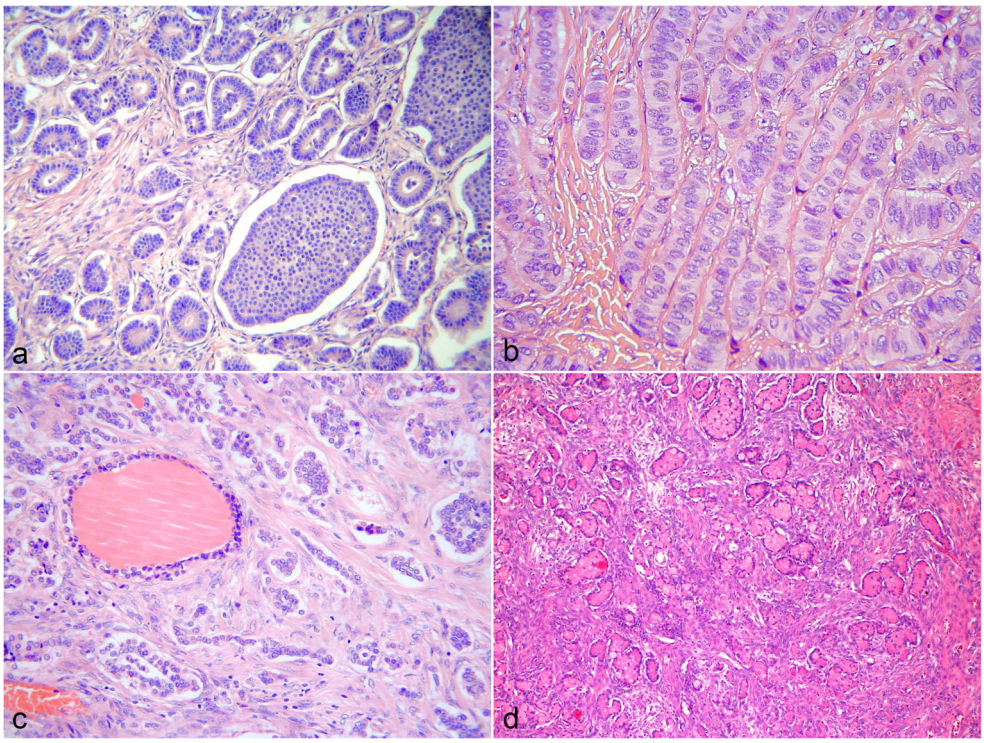

Fig. 1 Variants of ovarian carcinoid tumour. Insular carcinoid composed of nested and tubular arrangements of tumour cells (**a**), trabecular carcinoid composed of parallel ribbons of tumour cells (**b**), strumal carcinoid with admixture of trabecular carcinoid and occasional thyroid elements (*centre left*) (**c**) and mucinous (goblet cell) carcinoid composed of nests of cells with abundant intracytoplasmic mucin (**d**)

often CK20 positive and CK7 negative, although this is variable. Strumal carcinoids exhibit positive staining with neuroendocrine markers (carcinoid component) and thyroglobulin and thyroid transcription factor (TTF1) (thyroid component). The Ki67 proliferation index in primary ovarian carcinoid tumours of insular, trabecular and strumal types is usually less than 1%.

Behaviour of Ovarian Carcinoid Tumours

Primary ovarian insular, trabecular and strumal carcinoid tumours, especially when small and incidental microscopic findings within a teratoma, almost always exhibit a benign clinical behaviour [1, 13–16]. Mucinous carcinoids are rare but may exhibit aggressive behaviour with extraovarian spread [17].

Distinction Between Primary and Secondary Ovarian Carcinoid Tumour

As already discussed, most primary ovarian carcinoid tumours arise within teratomas or more uncommonly other ovarian neoplasms, and the presence of teratomatous elements (or one of the other neoplasms mentioned) is the strongest indicator of a primary ovarian carcinoid. Most, but not all, secondary ovarian carcinoid tumours occur in patients with a known history of carcinoid tumour (grade 1 or 2 NET), most commonly in the midgut [19]. Features in favour of a metastatic carcinoid tumour (as well as an absence of teratomatous elements) include bilateral ovarian involvement, ovarian surface involvement, a nodular pattern of growth, prominent lymphovascular space invasion and extraovarian spread (Table 2); these are features which are in favour of a metastatic ovarian neoplasm in general. Problems arise when faced with a unilateral ovarian carcinoid tumour without other teratomatous elements and an absence of any of the above features which are suggestive of a metastasis. In such cases, it is impossible to distinguish between a primary and secondary neoplasm, and clinicopathological correlation and radiological investigations are needed. There are no immunohistochemical markers which reliably distinguish between a primary and secondary insular, trabecular or mucinous carcinoid tumour within the ovary. The presence of admixed thyroid elements (strumal carcinoid) is indicative of a primary ovarian neoplasm.

Neuroendocrine Carcinomas of Ovary

As in other sites in the female genital tract, neuroendocrine carcinomas of the ovary are rare and are often, but not always, associated with an ovarian neoplasm of one of the common morphological types such as high-grade serous, mucinous or endometrioid carcinoma or Brenner tumour [20, 21]. While the classification of neuroendocrine carcinomas at other sites in the female genital tract (uterine corpus, cervix, vagina, vulva) was changed in WHO 2014 to the gastrointestinal terminology, the current ovarian classification rather confusingly does not reflect this. Included in the category of miscellaneous ovarian tumours is so-called “small-cell carcinoma of

Table 2 Distinction between primary and secondary ovarian carcinoid tumour

	Primary carcinoid	Secondary carcinoid
Presence of dermoid cyst (or rarely other ovarian neoplasm)	Usually yes	No
History of extraovarian neuroendocrine neoplasm	No	Sometimes
Laterality	Almost always unilateral	Often bilateral
Nodular pattern of ovarian involvement	Usually no	Often
Surface involvement	Usually no	Often
Lymphovascular invasion	Usually no	Often
Extraovarian involvement	Usually no	Often

pulmonary type" which is morphologically identical to pulmonary small-cell carcinoma [1]. The term small-cell carcinoma of neuroendocrine type is listed as a synonym, and it is better to use this terminology since the term "small-cell carcinoma of pulmonary type" has the potential to result in confusion for pathologists and clinicians alike. This is an extremely rare neoplasm with only a single series of 11 cases reported [20]. In that series, a majority were associated with another component, most commonly endometrioid adenocarcinoma or Brenner tumour. The behaviour was aggressive with 7 of 11 tumours having spread beyond the ovary at diagnosis. Five of seven patients with follow-up died at 1–13 months. Since this publication, there have been occasional reports of single cases, including a few arising within a mature cystic teratoma [22–24].

As well as the distinction from a variety of other "small round blue cell neoplasms" [25], ovarian small-cell carcinoma of pulmonary type must be distinguished from metastatic small-cell carcinoma, especially from the lung. Obviously, the presence of another component of ovarian neoplasm strongly favours a primary ovarian tumour. While a category of large-cell neuroendocrine carcinoma is not included in the current WHO Classification, these neoplasms uncommonly arise in the ovary, again often in association with an ovarian neoplasm of one of the more common subtypes [21]. The morphological features and immunohistochemical profile of ovarian small-cell and large-cell neuroendocrine carcinoma are essentially identical to the analogous neoplasms in the cervix (see below) and are not detailed here.

It should be noted that small-cell carcinoma of the ovary of hypercalcaemic type (SCCOHT) is not a neuroendocrine neoplasm and should not be confused with small-cell carcinoma of pulmonary type [26]. SCCOHT is generally negative with neuroendocrine markers, and recent studies [summarised in reference 26] have shown that almost 100% of these neoplasms contain deleterious germline or somatic mutations in a single gene, *SMARCA4*, a member of the SWI/SNF chromatin remodelling complex. *SMARCA4* encodes the BRG1 protein and loss of immunohistochemical staining with this marker may be extremely useful in diagnosing SCCOHT [26].

Other Neuroendocrine Tumours of Ovary

Rare paragangliomas/phaeochromocytomas (another neuroendocrine neoplasm) have also been reported within the ovary [27]. Some of these have exhibited malignant behaviour with extraovarian spread.

Neuroendocrine Tumours of Endometrium

General Comments

The 2014 WHO Classification of endometrial neuroendocrine tumours includes low-grade neuroendocrine tumour (carcinoid tumour) and high-grade neuroendocrine carcinoma (small-cell and large-cell neuroendocrine carcinoma) [1]. Low-grade neuroendocrine tumours are extremely rare with only occasional reports in the literature and will not be discussed further [28, 29]. High-grade neuroendocrine carcinomas of the endometrium are uncommon tumours, accounting for <1% of all endometrial carcinomas. There are now over 100 cases reported in the English language literature with a significant majority associated with another histotype of carcinoma [30–72].

Clinical Features

Patients with neuroendocrine carcinoma of the endometrium present most commonly with vaginal bleeding, similar to other uterine malignancies. Rarely, there is an associated paraneoplastic syndrome such as Cushing's syndrome, retinopathy or glomerulopathy [35, 53, 62, 63]. The tumours affect a wide age range (23–78 years in literature) with an average age of 57 years [58].

Pathological Features

Typically, these grossly comprise a large endometrial-based mass, often with deep myometrial invasion. There are no pathognomic gross features.

In many cases, these tumours occur in association with a more typical form of endometrial adenocarcinoma (endometrioid being most common followed by serous carcinoma); less frequently, they occur as a pure histotype. Most of the case reports and small series focus on small-cell neuroendocrine carcinoma, although in the largest series to date, a minority of endometrial neuroendocrine carcinomas were of the small-cell histotype with the majority being of large cell type [58]. The morphological features are essentially identical to the corresponding tumours within the uterine cervix (see below). Similar to the cervix, some tumours have areas of both large-cell and small-cell morphology, and in other cases, the features are overlapping.

Immunohistochemistry

Usually, endometrial neuroendocrine carcinomas are positive for at least one neuroendocrine marker (synaptophysin, chromogranin, CD56) in at least 10% of the tumour cells. However, CD56 is a very non-specific marker and in the context of only positivity with this marker (without concurrent expression of synaptophysin or chromogranin), a neuroendocrine carcinoma should be doubted. Conversely, with a tumour lacking immunohistochemical expression of any neuroendocrine marker, but with classic small-cell carcinoma morphology, the diagnosis of a neuroendocrine carcinoma can be rendered (similar comments pertain in the cervix- see below). Most neuroendocrine carcinomas are positive with broad spectrum cytokeratins, sometimes with a paranuclear "dot-like" pattern. As in the cervix, endometrial neuroendocrine carcinomas may be positive with TTF1. However, TTF1 positivity is probably less common than in cervical neuroendocrine carcinomas; in the largest immunohistochemical study of endometrial neuroendocrine carcinomas, only one of 18 cases was focally positive with TTF1 [58]. p16 is positive in the majority of endometrial neuroendocrine carcinomas, including some with strong and diffuse immunoreactivity [58]. Therefore, diffuse p16 immunoreactivity is not useful in the distinction between a cervical and endometrial neuroendocrine carcinoma; as discussed later, cervical neuroendocrine carcinomas are usually diffusely positive with p16 secondary to the presence of high-risk human papillomavirus (HPV). Endometrial neuroendocrine carcinomas are not associated with HPV. One study showed loss of expression of mismatch repair proteins to be common in endometrial neuroendocrine carcinomas (44%), with the most common pattern being loss of MLH1/PMS2, presumably due to epigenetic silencing of *MLH1* via promoter methylation, although this has not been fully investigated [58].

Prognosis

Neuroendocrine carcinomas of the endometrium often present with metastatic disease and are associated with poor progression-free and overall survival; however, in the largest study (which included 25 neuroendocrine carcinomas, predominantly admixed with other variants of endometrial adenocarcinoma), 28% of patients were alive 5 years after diagnosis [58].

Differential Diagnosis

High-grade neuroendocrine carcinomas of the endometrium with a small-cell morphology must be distinguished from other small round blue cell tumours that may involve the endometrium, including lymphoma, malignant melanoma, neuroblastoma, rhabdomyosarcoma and Ewing family of tumours. The identification of another tumour component and appropriate immunohistochemistry will aid in this distinction.

Secondary involvement of the uterine corpus by a neuroendocrine carcinoma arising in another site, either distant or local such as the cervix, should be excluded, especially if there is no other tumour component. While immunohistochemistry will likely not aid significantly in this differential diagnosis, HPV testing can help in the differential diagnosis between a cervical and an endometrial neuroendocrine carcinoma, with cervical tumours often being HPV positive. Endometrial neuroendocrine carcinomas have been HPV negative when testing has been undertaken.

High-grade endometrial carcinomas with a solid or nested growth pattern (including grade 3 endometrioid and serous carcinomas) may result in consideration of a neuroendocrine carcinoma, especially of large cell type. The neuroendocrine markers synaptophysin and chromogranin are not significantly positive in endometrioid and serous carcinomas, although occasionally focal staining (usually <10% of tumour cells) is seen. One of the major differential diagnoses of endometrial large-cell neuroendocrine carcinoma is endometrial undifferentiated carcinoma or the undifferentiated component of dedifferentiated carcinoma, the latter neoplasm comprising an admixture of low-grade endometrioid carcinoma and undifferentiated carcinoma. Undifferentiated carcinomas generally show no nested architecture but have a totally diffuse sheet-like growth, often with a prominent dyscohesive appearance. They may be positive for neuroendocrine markers, but this is usually focal involving <10% of tumour cells [73].

Neuroendocrine Tumours of Uterine Cervix

General Comments

The cervix is the commonest site for neuroendocrine carcinomas in the female genital tract. The 2014 WHO Classification categorises cervical neuroendocrine neoplasms as low-grade neuroendocrine tumour (encompassing what were previously referred to as carcinoid tumour and atypical carcinoid tumour)

and high-grade neuroendocrine carcinoma (encompassing what were previously referred to as small-cell carcinoma and large-cell neuroendocrine carcinoma [1]. A category of adenocarcinoma admixed with neuroendocrine carcinoma is also listed. The current terminology is a change to the 2003 WHO Classification where categories of carcinoid tumour, atypical carcinoid tumour, small-cell carcinoma and large-cell neuroendocrine carcinoma were included [2]. Given this relatively recent change in terminology, in order to avoid confusion, we recommend pathologists to at present use both the WHO 2003 and 2014 categories when reporting a cervical neuroendocrine carcinoma, for example, high-grade neuroendocrine carcinoma (small-cell neuroendocrine carcinoma). The term small-cell neuroendocrine carcinoma is preferred to small-cell carcinoma since a small-cell variant of squamous carcinoma occurs in the cervix and use of the term small-cell carcinoma (without further explanation) can result in confusion. This is important since the management of small-cell neuroendocrine carcinoma and large-cell neuroendocrine carcinoma differs significantly from non-neuroendocrine carcinomas.

In the cervix, small-cell neuroendocrine carcinoma is the most common of these neoplasms followed by large-cell neuroendocrine carcinoma; well-differentiated neuroendocrine tumours (carcinoid and atypical carcinoid) are extremely rare and will not be discussed further [31, 74–79]. Cervical high-grade neuroendocrine carcinomas are mostly HPV-associated neoplasms, the most common HPV types being 16 and 18; in some, but not all, studies, HPV18 has been found more commonly than HPV 16 [77, 79]. There is an association between cervical neuroendocrine carcinomas and premalignant or malignant cervical glandular lesions (hence the WHO category of adenocarcinoma admixed with neuroendocrine carcinoma); foci of CIN or squamous carcinoma are also occasionally admixed with neuroendocrine carcinomas. Occasional neoplasms are composed of an admixture of small-cell neuroendocrine carcinoma and large-cell neuroendocrine carcinoma, and in some cases, the morphological features are such that it may be difficult to categorise an individual neoplasm as small-cell neuroendocrine carcinoma or large-cell neuroendocrine carcinoma. As well as alignment with the terminology used for gastrointestinal neuroendocrine neoplasms, this is an additional reason for using the term high-grade neuroendocrine carcinoma.

Clinical Features

Patients with cervical neuroendocrine carcinomas usually present in a similar manner to other cervical malignancies. There is often metastatic disease at presentation.

Pathological Features

There are no characteristic gross features of cervical neuroendocrine carcinomas. Small-cell neuroendocrine carcinoma is characterised by the presence of a monotonous population of cells with ovoid or somewhat spindled hyperchromatic nuclei, often exhibiting moulding, and scanty cytoplasm. There is usually abundant mitotic and apoptotic activity. There may be extensive crush artefact, nuclear fragmentation and necrosis. The growth pattern is usually predominantly diffuse but nests, trabeculae, pseudoglandular and rosette-like structures are sometimes present.

Large-cell neuroendocrine carcinoma is characterised by large polygonal cells with a low nuclear to cytoplasmic ratio, nuclei with coarse chromatin and prominent nucleoli and high mitotic activity. Insular/nested, trabecular, pseudoglandular and solid growth patterns are often present, either alone or in combination. There is often extensive geographic necrosis. Nuclear palisading may be present around the periphery of cell nests, and eosinophilic cytoplasmic granules are present in some cases.

Figure 2 illustrates a combined cervical adenocarcinoma and high-grade neuroendocrine carcinoma (small-cell neuroendocrine carcinoma).

Immunohistochemistry

Small-cell neuroendocrine carcinoma is variably positive with the neuroendocrine markers chromogranin, CD56,

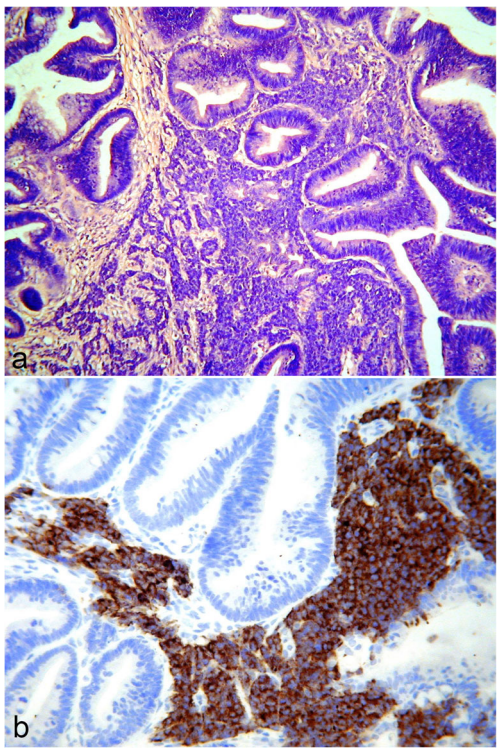

Fig. 2 Cervical combined adenocarcinoma and high-grade neuroendocrine carcinoma (small-cell neuroendocrine carcinoma) (**a**). Immunohistochemical staining for synaptophysin shows the adenocarcinoma component to be negative and the neuroendocrine component to be diffusely positive (**b**)

synaptophysin and PGP9.5. CD56 and synaptophysin are the most sensitive neuroendocrine markers, but CD56 lacks specificity. Chromogranin is the most specific neuroendocrine marker but lacks sensitivity with only about 50% of small-cell neuroendocrine carcinoma being positive [80]. Chromogranin positivity may be very focal with punctuate cytoplasmic immunoreactivity which is only visible on high power magnification. A diagnosis of small-cell neuroendocrine carcinoma can be made in the absence of neuroendocrine marker positivity if the morphological appearances are typical. Small-cell neuroendocrine carcinoma may be only focally positive (often punctuate cytoplasmic staining) or even negative with broad spectrum cytokeratins. A diagnosis of large-cell neuroendocrine carcinoma requires neuroendocrine marker positivity, and most of these neoplasms are diffusely positive with broad spectrum cytokeratins.

A high percentage of primary cervical high-grade neuroendocrine carcinomas are TTF1 positive, including some with diffuse immunoreactivity, and this marker is of no value in distinction from a pulmonary metastasis [80]. Most cervical high-grade neuroendocrine carcinomas are diffusely positive with p16 due to the presence of high-risk HPV [80]. Peptide hormones, including ACTH, serotonin, somatostatin, calcitonin, glucagon and gastrin, have been demonstrated in some cervical high-grade neuroendocrine carcinomas [80].

Prognosis

Cervical high-grade neuroendocrine carcinomas are highly aggressive neoplasms with a propensity for widespread systemic metastasis; even neoplasms with a minor component of high-grade neuroendocrine carcinoma may behave aggressively. The overall prognosis is poor with survival rates of 25–35% [31, 74–79, 81•]. Involvement of regional and distant lymph nodes, lung, liver, bone and brain is common.

Differential Diagnosis

As in the endometrium, high-grade neuroendocrine carcinomas with small-cell morphology must be distinguished from other small round blue cell tumours that may involve the cervix, including lymphoma, malignant melanoma, neuroblastoma, rhabdomyosarcoma and Ewing family of tumours. Another differential diagnosis is a small-cell variant of squamous carcinoma. Diffuse p63 nuclear positivity is useful in confirming a small-cell variant of squamous carcinoma rather than small-cell neuroendocrine carcinoma, although occasional small-cell and large-cell neuroendocrine carcinomas exhibit p63 nuclear immunoreactivity [80, 82]. Small-cell variants of squamous carcinoma are negative with neuroendocrine markers, while most, but as discussed not all, small-cell neuroendocrine carcinomas are positive with at least one of the markers. Large-cell neuroendocrine carcinomas should be distinguished from poorly differentiated squamous and adenocarcinomas and undifferentiated carcinomas involving the cervix. This depends on the demonstration of significant neuroendocrine marker positivity in large-cell neuroendocrine carcinomas. As discussed previously, HPV testing can help in the differential diagnosis between a cervical neuroendocrine carcinoma and neuroendocrine carcinomas arising at other sites, including the endometrium, since cervical tumours are often HPV positive.

Neuroendocrine Tumours of Vulva and Vagina

Since these are extremely rare, they will only be discussed briefly. The WHO 2014 Classification includes categories of high-grade neuroendocrine carcinoma at both sites and Merkel cell carcinoma in the vulva [1]. High-grade neuroendocrine carcinoma of the vulva or vagina is essentially a diagnosis of exclusion, as the histological and immunophenotypic features are identical to those of neuroendocrine carcinomas arising at other sites. Therefore, before rendering a diagnosis of a neuroendocrine carcinoma in the vulva or vagina, a metastasis from elsewhere needs to be excluded.

Primary neuroendocrine carcinomas of the vulva are extremely rare, the majority of reported cases representing cutaneous Merkel cell carcinomas [83–90]. As far as we are aware, there has only been a single reported example of a vulvar small-cell neuroendocrine carcinoma and this was associated with a component of squamous carcinoma [91]. To our knowledge, no pure primary neuroendocrine carcinoma of the vulva has been reported. Primary neuroendocrine carcinomas of the vagina are also extremely rare, and most have been of small-cell type; like small-cell neuroendocrine carcinomas arising at other sites, they often present with metastatic disease and display extremely aggressive behaviour [92–95].

Ancillary Studies Useful in Determining Site of Origin of Neuroendocrine Tumour

The management of metastatic neuroendocrine tumours is determined by the primary site and tumour grade i.e. well-differentiated (carcinoid) versus poorly differentiated (small-cell or large-cell neuroendocrine carcinoma). At present, metastatic high-grade neuroendocrine carcinomas are generally treated using similar chemotherapy regimens regardless of primary site. In contrast, it has become important to try to establish the primary site of well-differentiated tumours, as their behaviour and response to certain treatments vary according to site of origin [96]. For example, cytotoxic chemotherapy is generally not effective in the treatment of jejunal and ileal (midgut) WDNETs but is used to treat advanced pancreatic WDNETs [97]. Similarly, the indications for use

of targeted therapies, such as everolimus, vary according to the primary site of the tumour [96, 98, 99]. While modern imaging techniques can accurately identify the site of origin in most cases of advanced disease, in 15–20% of cases, the primary site cannot be established despite detailed radiological evaluation [96, 98]. To this end, immunohistochemistry provides an alternative and relatively cost-effective strategy to try to establish the primary site [96]. As always, use of a panel of markers is more useful than the application of single markers. Some of the main diagnostically useful antibodies for helping to determine the primary sites of a WDNET are discussed below and summarised in Table 3.

TTF1

This marker is most useful in distinguishing pulmonary carcinoids (this terminology is still used for lung neoplasms) from WDNETs of intestinal and pancreatic origin. TTF1 positivity has been reported as being highly specific for pulmonary carcinoids, but sensitivity varies with between 0 and 95% of tumours (both typical and atypical lung carcinoids) showing positivity in various studies [100–105] with a reported mean of 32% based on a recent meta-analysis [106].

In contrast, TTF1 positivity is exceptionally rare in gastrointestinal and pancreatic WDNETs [103, 106]. Most (86%) pulmonary small-cell neuroendocrine carcinomas are positive for TTF1, although only 36% of large-cell neuroendocrine carcinomas are positive. However, this is not specific for pulmonary neuroendocrine carcinomas since TTF1 expression occurs in many extrapulmonary neuroendocrine carcinomas (see section on "Neuroendocrine tumours of uterine cervix"), therefore limiting its diagnostic utility in this setting [104, 106].

CDX2

CDX2 is a useful marker of WDNETs of intestinal origin. The expression rates vary according to site within the gastrointestinal tract with the highest rates being reported in the jejunum and ileum (90%) and appendix (93%). Expression is less common in the duodenum (31%), colon (25%), rectum (29%), stomach (14%) and pancreas (16%) [106–111]. Positivity in lung carcinoids is extremely rare (approximately 3%) [100, 103, 106–111]. Thus, CDX2 is highly sensitive for jejunal, ileal and appendiceal WDNETs with moderate specificity and is particularly useful for differentiating WDNETs of intestinal and pulmonary origin. A study of primary ovarian carcinoids showed that tumours with insular but not trabecular growth patterns were commonly positive for CDX2 (71%) [18]. Insular ovarian carcinoids are morphologically and immunophenotypically identical to small intestinal or midgut WDNETs, and this likely reflects the fact that ovarian insular carcinoids arise from intestinal elements within teratomas.

Paired Box Gene (PAX) Family

PAX8, more specifically polyclonal PAX8, positivity is seen in 32–88% of primary and metastatic pancreatic neuroendocrine tumours. Positivity has also been demonstrated in 60% of rectal, 77% of duodenal and 15% of gastric neuroendocrine tumours. Rare positivity has been documented in appendiceal neuroendocrine tumours. PAX8 is negative in jejunal and ileal tumours, but up to 9% of lung tumours are positive [112–117]. Because monoclonal PAX8 is negative in normal pancreatic islets, it has been suggested that polyclonal PAX8 cross-reacts with another member of the PAX family, PAX6, which is involved in islet development [115, 118]. In this regard, the PAX6 expression profile in WDNETs is very similar to PAX8, but it may have slightly greater specificity for pancreatic tumours compared to PAX8 [104].

Isl-1

Islet-1 (Isl-1) is a transcription factor involved in pancreatic development, including endocrine cells within the islets. Isl-1 is expressed in a high percentage of pancreatic WDNETs. Expression is also seen in rectal (86%) and duodenal (86%)

Table 3 Summary of commonly used immunohistochemical markers for determining the primary site of well-differentiated neuroendocrine carcinomas

	Lung	Jejunum/ileum/appendix	Rectum	Pancreas	Duodenum
TTF1	+	−	−	−	−
CDX2	−	+[c]	+/−	−/+	+/−
Isl-1	−	−	+	+	+
PAX8	−	−	+	+	+
PDX1	−	−[a]	−/+[b]	+/−	+/−
PSAP	−	−	+	−	−

+ positive most cases(typically >90%), − negative in most cases (>90%), +/− positive in 25–75%, −/+ rare positivity (typically <25%)

[a] Limited studies have documented staining in appendiceal NETS

[b] Only a few cases have been studied

[c] Expression may be seen in ovarian WDNETs with insular growth pattern

tumours. Isl-1 positivity is also seen in a small percentage of lung carcinoids and appendiceal WDNETs. By contrast, expression has been reported in only 3% of jejunal and ileal tumours [104, 110, 113, 119–122]. Overall, Isl-1 is a sensitive marker for pancreatic, rectal and duodenal WDNETs, and positivity for this marker effectively excludes an origin in the jejunum or ileum [104].

PDX1

Pancreatic and duodenal homeobox 1 (PDX1) is a transcription factor expressed in pancreatic development and is normally expressed in islet cells. Expression also occurs in duodenal epithelium in adults. A recent review has described positive staining in 54% of pancreatic and 56% of duodenal NETs, respectively. Expression in lung NETs is rare (approximately 6%) and has not been described in ileal or jejunal NETs. There is relatively limited data for other sites, but some gastric, appendiceal and rectal NETs have been shown to be positive for PDX1 [96, 101, 103, 106, 120].

PSAP

While PSAP is most commonly used to determine if a carcinoma is of prostatic origin, expression occurs in 80–90% of rectal neuroendocrine tumours and in up to 20% of jejunal and ileal tumours [104, 110, 123, 124].

p16 and HPV Studies

While most cervical high-grade neuroendocrine carcinomas are diffusely positive with p16 due to the association with high-risk HPV, this marker is of limited value in determining the site of origin since neuroendocrine carcinomas arising at many sites can be diffusely positive secondary to non-HPV-related mechanisms which result in disruption of the retinoblastoma pathway. For example, a recent study of 19 high-grade neuroendocrine carcinomas of the head and neck region (all were HPV negative) showed 14 to be diffusely p16 positive [125•]. The demonstration of HPV within a tumour by molecular methods may be of value in establishing a cervical origin when this is in the differential diagnosis, although neuroendocrine carcinomas at other sites are occasionally HPV related.

Conclusions

Neuroendocrine neoplasms are uncommon or rare at all sites in the female genital tract and often, but not always, arise in association with other tumours. In the ovary, carcinoid tumours which usually arise in dermoid cysts are the most common neuroendocrine neoplasm and almost always behave in a benign fashion. In the uterus (endometrium and cervix), high-grade neuroendocrine carcinomas are most common and exhibit extremely aggressive behaviour. The terminology of neuroendocrine tumours at all sites in the female genital tract (endometrium, cervix, vagina, vulva) except for the ovary has evolved in recent years to match that used for gastrointestinal neuroendocrine neoplasms. It is hoped that the next WHO Classification will change the terminology of ovarian neuroendocrine neoplasms to standardise the terminology at all sites within the female genital tract. Given the recent advent of multidisciplinary teams dealing with neuroendocrine neoplasms at all sites, the development of standardised terminologies across various sites will be an important development in patient care.

Compliance with Ethical Standards

Conflict of Interest Brooke E. Howitt, Paul Kelly, and W. Glenn McCluggage declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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