Arch Gynecol Obstet (2016) 293:659–665
DOI 10.1007/s00404-015-3865-0

GYNECOLOGIC ONCOLOGY

Neuroendocrine tumors in the ovary: histogenesis, pathologic differentiation, and clinical presentation

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Received: 6 November 2014 / Accepted: 18 August 2015 / Published online: 26 August 2015

Abstract
Objective Primary neuroendocrine tumors in the ovary are rare. These tumors arise from the neuroendocrine cell system of ovarian stroma and surface epithelium, and may also arise from teratoma. We present four primary ovarian neuroendocrine tumors and compare clinicopathologic findings based on tumor histogenesis and site of origin.
Design Four primary ovarian neuroendocrine tumors were identified from our 10-year departmental archives. H&E slides and immunostains were reviewed and the diagnoses were confirmed. Clinical history, imaging studies, and follow-up data were obtained from medical records.
Results Patients' ages ranged from 26 to 63. All patients presented with abdominal discomfort and unilateral or bilateral ovarian masses. MRI and CT scans from cases 1 and 2 revealed a solid ovarian mass with no extra-ovarian extension. In case 1, the patient also had a cystic mass in the opposite ovary and an elevated urine 5-HIAA. Microscopically, case 1 revealed a well-differentiated carcinoid tumor with no surface epithelial involvement, and a mature teratoma in the contralateral ovary. Case 2 revealed a stromal carcinoid within the ovarian parenchyma. Imaging studies from cases 3 and 4 showed large complex masses with peritoneal implants and ascites. In both cases 3 and 4, tumor grossly involved both ovarian parenchyma and surface epithelium with multiple pelvic implants. In addition, liver metastases were present in case 4. Microscopically, these tumors were poorly differentiated carcinoma with neuroendocrine differentiation. Histologic sections revealed extensive necrosis, and both cases showed positivity for neuroendocrine markers.
Conclusions Primary neuroendocrine tumors in the ovary are rare and consist of a group of heterogeneous malignancies that express similar immunohistochemical markers. Primary neuroendocrine tumors that are limited to the ovarian parenchyma often arise from ovarian stroma and teratoma, and are carcinoid tumors with a good prognosis. Neuroendocrine tumors that arise from surface epithelium or dedifferentiate from de novo carcinoma often involve both ovarian stroma and surface epithelium and clinically present as aggressive malignancies with poor prognoses.

Keywords Ovary · Neuroendocrine tumor · Carcinoid · Carcinoma

Introduction

Neuroendocrine tumors in the ovary are rare and account for less than 1–2 % of malignant ovarian neoplasms [1, 2]. As in other organs, neuroendocrine tumors in the ovary consist of a spectrum of malignancies that arise from the diffuse neuroendocrine cell system. Clinical presentation and prognosis are dependent on histologic subtype and site of origin.

In pathologic diagnoses, neuroendocrine neoplasms of different histological subtypes and sites of origins are grouped together because these tumors express similar generic neuroendocrine markers such as synaptophysin, chromogranin, and CD56. However, the morphologic

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features, pathologic differentiation, and biologic behavior are quite different and highly dependent on histogenesis and tumor site of origin [2].

In general, well-differentiated neuroendocrine tumors arise from the neural crest tissue present in ovarian stroma or within teratoma. As in the aerodigestive tract and pancreas, well to moderately differentiated neuroendocrine tumors of the ovary are carcinoid/atypical carcinoid tumors. These rare ovarian neuroendocrine tumors lack significant nuclear atypia, high mitotic counts, and necrosis. Clinically, patients may show neuroendocrine symptoms [3]. Given their degree of differentiation, carcinoid and atypical carcinoid tumors of the ovary are thought to be indolent; however, the rarity of these tumors limits the data available on clinical outcomes.

In contrast, poorly differentiated neuroendocrine carcinomas of the ovary are highly atypical with high mitotic rates and focal or extensive necrosis. They often involve the surface of the ovary and extra-ovarian pelvic tissue [4, 5]. Their histologic origin is thought to be from ovarian surface epithelial cells or dedifferentiation from de novo carcinomas [6, 7].

Recently, it has suggested that neuroendocrine neoplasms of the ovary should be classified into two groups: (1) carcinoid tumors arising from the ovarian stroma and (2) non-small cell neuroendocrine carcinoma [1]. Neuroendocrine carcinomas have often been associated with epithelial neoplasms [5, 8]. This phenomenon suggests that they may directly arise from epithelial cells or dedifferentiate from carcinomas that are mainly of epithelial origin. In addition to their distinct morphological features, clinically these two groups of neuroendocrine tumors also show different biological behavior [5, 9]. Herein, we describe four cases of primary neuroendocrine tumors, two well-differentiated (carcinoid tumors) and two poorly differentiated neuroendocrine carcinomas, to emphasize that histomorphology, biologic behavior, and clinical prognosis are closely related to histogenesis and site of origin.

Materials and methods

Clinical data and pathological sections from 2001 to 2014 were retrieved from electronic medical records and pathology archives at our institute. We identified four ovarian neuroendocrine neoplasms based on pathologic examination of surgically resected tissue specimens. At our institute, 100 salpingo-oophorectomies were performed on average for ovarian neoplasms, and more than 350 cases of hysterectomy with salpingo-oophorectomy were performed for either uterine lesions or lesions of the ovary/fallopian tube or both.

All pathology specimens were routinely fixed in 10 % neutral formalin and embedded in paraffin. Four micron sections were prepared for routine hematoxylin and Eosin stain and immunohistochemical stains when necessary. Immunohistochemistry stain was performed after deparaffinizing and rehydration, followed by standard peroxidase immunohistochemistry techniques using Ventana Banchmaker XT Autostainer (Ventana ULTRA system, Tucson, AZ, USA). The antibodies for CD56, synaptophysin, and chromogranin were obtained from Ventana, which were prediluted for Autostainer.

Results

Clinical data

Clinical presentations and demographic characteristics are summarized in Table 1. Four patients with primary ovarian neuroendocrine tumors were identified. Their ages ranged from 26 to 64. All four patients presented with abdominal discomfort and either bilateral (cases 1, 3, and 4) or unilateral (case 2) ovarian masses. Clinically, neuroendocrine symptoms, such as persistent facial flushing and episodes of hypertension, were noted in case 1. This patient also had elevated urine 5-HIAA. Two patients (cases 3 and 4) presented with an abdominal mass accompanied by rapidly deteriorating general condition and worsening ascites. On the magnetic resonance imaging (MRI) or computed tomography scan (CTS) studies, cases 1 and 2 showed a solid ovarian mass with no ascites or other lesions (Fig. 1a). In both cases 3 and 4, in addition to large complex ovarian masses, pelvic implants and ascites were also present (Fig. 1b). In cases 1, 2, and 3, there were no tumoral lesions identified in the gastrointestinal tract, pancreatic-hepatobiliary system, or lungs on imaging studies. In case 4, a 3.5 × 4.0 cm metastatic tumor was present in the liver.

Intraoperatively, cases 1 and 2 showed solid and/or cystic ovarian masses with no other pelvic lesions. The vermiform appendix and omentum appeared normal. In cases 3 and 4, the bilateral ovaries revealed large complex tumor masses. Case 3 involved widespread implants in the pelvic peritoneum, omentum, and small bowel loops. In case 4, several small white firm nodules were identified in the omentum (Table 2).

Pathologic findings

Grossly, in case 1, the right ovary was replaced by an 8.0 cm mass with a smooth serosal surface. Serial sections revealed yellow-tan, firm tumor parenchyma with no hemorrhage, necrosis, or penetration of the capsule

Table 1 Clinical demographic characteristics and presentations

Cases	Age	Clinical presentation	Imaging studies
1	40	Abdominal discomfort. Persistent facial flushing, episodes of hypertension and elevated urine 5-HIAA	Solid mass in right ovary (8 cm) and cystic mass in left ovary
2	26	Abdominal discomfort and abnormal Pap smear	13 cm cystic mass in left ovary on MRI examination
3	63	Abdominal bloating with rapidly developing ascites, nausea and vomiting	Large complex pelvoabdominal mass involving bilateral ovaries, multiple implants and ascites
4	32	Abdominal pain	Heterogenous 14 cm complex mass arises from left ovary and extends into the lower abdomen left of midline with multiple tumor implants in pelvis and abdomen. Liver with a 4 cm metastatic tumor

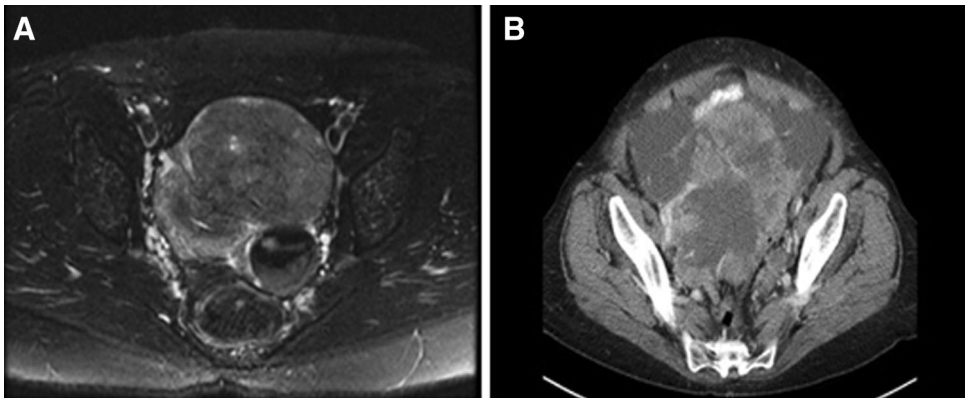

Fig. 1 Imaging studies. **a** MRI photo from case 1. **b** CTS photo from case 3

Table 2 Pathologic findings, treatment, and follow-up

Cases	Age	Pathologic findings	Treatment and follow-up
1	40	WDNT in right ovary, benign cystic teratoma in left ovary	S/P bilateral salpingo-oophorectomy, appendectomy and total hysterectomy for 9 months, negative for recurrent or residual disease
2	26	WDNT	S/P unilateral salpingo-oophorectomy for 12 years, negative for recurrent or residual disease
3	63	PDNC	S/P bilateral salpingo-oophorectomy, pelvic lymph node dissection and implant resection for 9 months. S/P chemotherapy. Alive and under surveillance
4	32	PDNC	S/P bilateral salpingo-oophorectomy, omentum implant excision and S/P chemotherapy. Follow-up was stopped 6 months after surgery

WDNT well-differentiated neuroendocrine tumor, *PDNC* poorly differentiate neuroendocrine carcinoma

(Fig. 2a). The contralateral ovary was also enlarged but soft, and sections revealed features typical of a mature cystic teratoma with hair and oily sebaceous material. In case 2, the ovary was enlarged and firm with no lesions on the serosal surface. Sections showed ovarian parenchyma that was partially replaced by brown tumor tissue with foci of small cystic structures. In cases 3 and 4, the tumors comprised of large masses with irregular tumor nodules protruding through the serosal surfaces. Areas of hemorrhage, necrosis, and secondary cystic degeneration were also present (Fig. 3a).

In case 1, microscopic examination showed the right ovary mass with typical features of a carcinoid tumor. The tumor cells were uniform with small nucleoli and fine 'salt and pepper' chromatin. Tumor growth occurred as nests, tubular, and trabecular architectural patterns and extended throughout the ovary but with capsular sparing (Fig. 2b, c). In the left ovary, mature teratoma (dermoid cyst) components with no neuroendocrine elements were seen. In case 2, the ovary was partially replaced by a teratoma containing thyroid and neuroendocrine tissue. The neuroendocrine tumor components were growing in an insular pattern, and as nests of cells or clusters of single cells accompanied by a desmoplastic stromal reaction (Fig. 2e). In both cases 1 and 2, the tumor cells were positive for neuroendocrine markers, synaptophysin, and chromogranin (Fig. 2d, f).

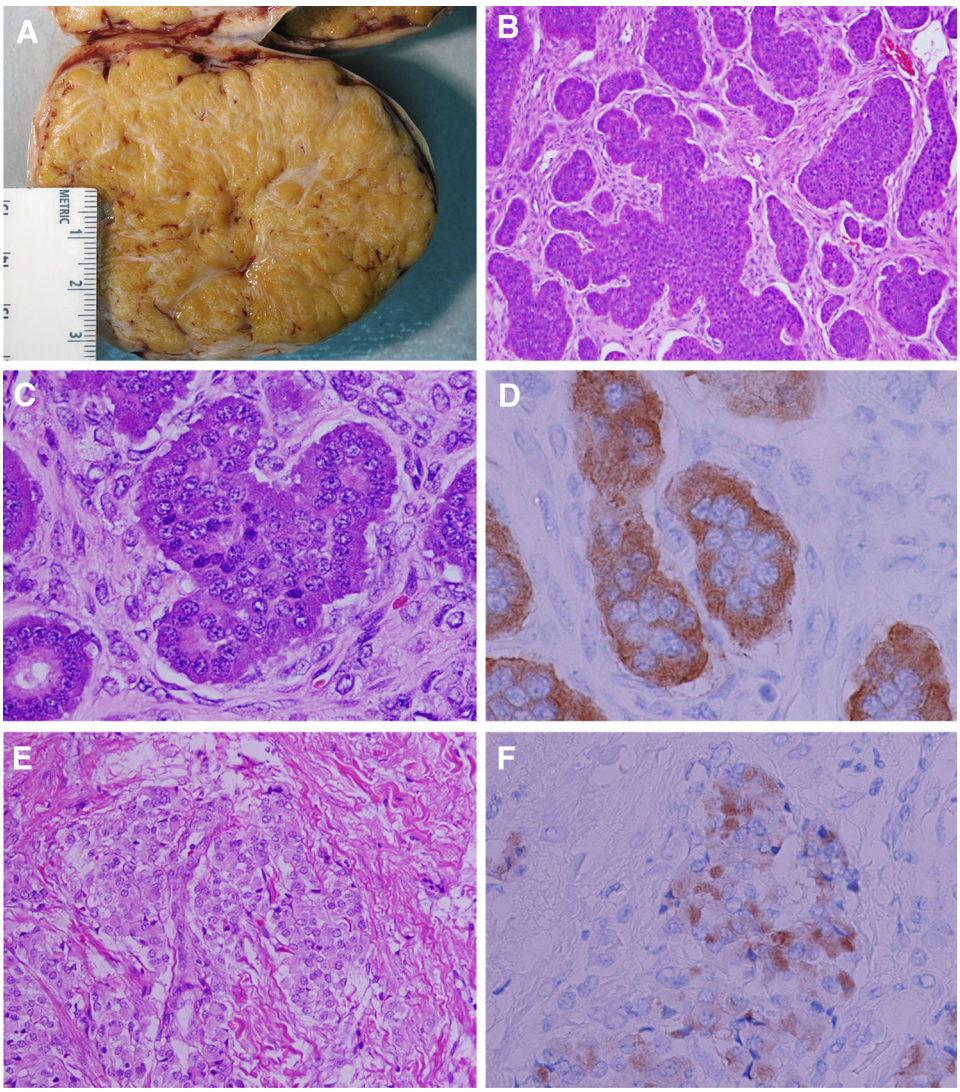

Fig. 2 Gross and microscopic findings of well-differentiated neuroendocrine tumor in the ovary. **a**–**d** case 1. **a** Gross section of tumor reveals a firm, yellow, and solid tumor that involves the entire ovarian parenchyma. **b**, **c** Microscopic examination shows tumor that grows in nests and trabeculae. The tumor cells contain eosinophilic cytoplasm, uniform nuclei with fine "salt and pepper" chromatin. **d** Tumor cells are positive for synaptophysin. **e** and **f** case 2. **e** Nests of well-differentiated neuroendocrine tumor cells in the ovary in a background of fibrotic stroma. **f** The tumor cells show positivity in the cytoplasm for synaptophysin

Microscopically, cases 3 and 4 showed poorly differentiated carcinoma with neuroendocrine features. The tumors diffusely infiltrated the ovarian parenchyma and penetrated the capsule. The tumor cells revealed marked nuclear pleomorphism, brisk mitoses, and apoptotic figures (Fig. 3b, c). Large areas of solid necrosis or comedo type necrosis were present (Fig. 3d, f). Although these tumors were poorly differentiated, they still maintained the cytological features of neuroendocrine differentiation and were focally positive for neuroendocrine markers such as synaptophysin and CD56.

Treatment and clinical follow-up

Therapy consisted of bilateral salpingo-oophorectomy with hysterectomy in case 1 and bilateral salpingo-oophorectomy with hysterectomy plus resection of tumor implants and dissection of pelvic lymph nodes in cases 3 and 4. For case 2, unilateral salpingo-oophorectomy was performed, and hysterectomy was also done for severe cervical squamous dysplasia. Adjuvant chemotherapy was given to patients 3 and 4, 2 weeks after resection. Upon follow-up, cases 1 and 2 were disease free after surgery (at 10 months for case 1 and at 12 years for case 2). Case 3 status is post chemotherapy and currently under surveillance (at 9 months follow-up), and follow-up for case 4 was stopped 6 months after surgery and chemotherapy.

Discussion

In recent years, studies have indicated that ovarian neoplasms are heterogeneous and tumor histogenesis is closely related with tumor differentiation pathway [10]. Primary neuroendocrine tumors in the ovary are rare. Clinical presentation and outcome are variable due to tumor

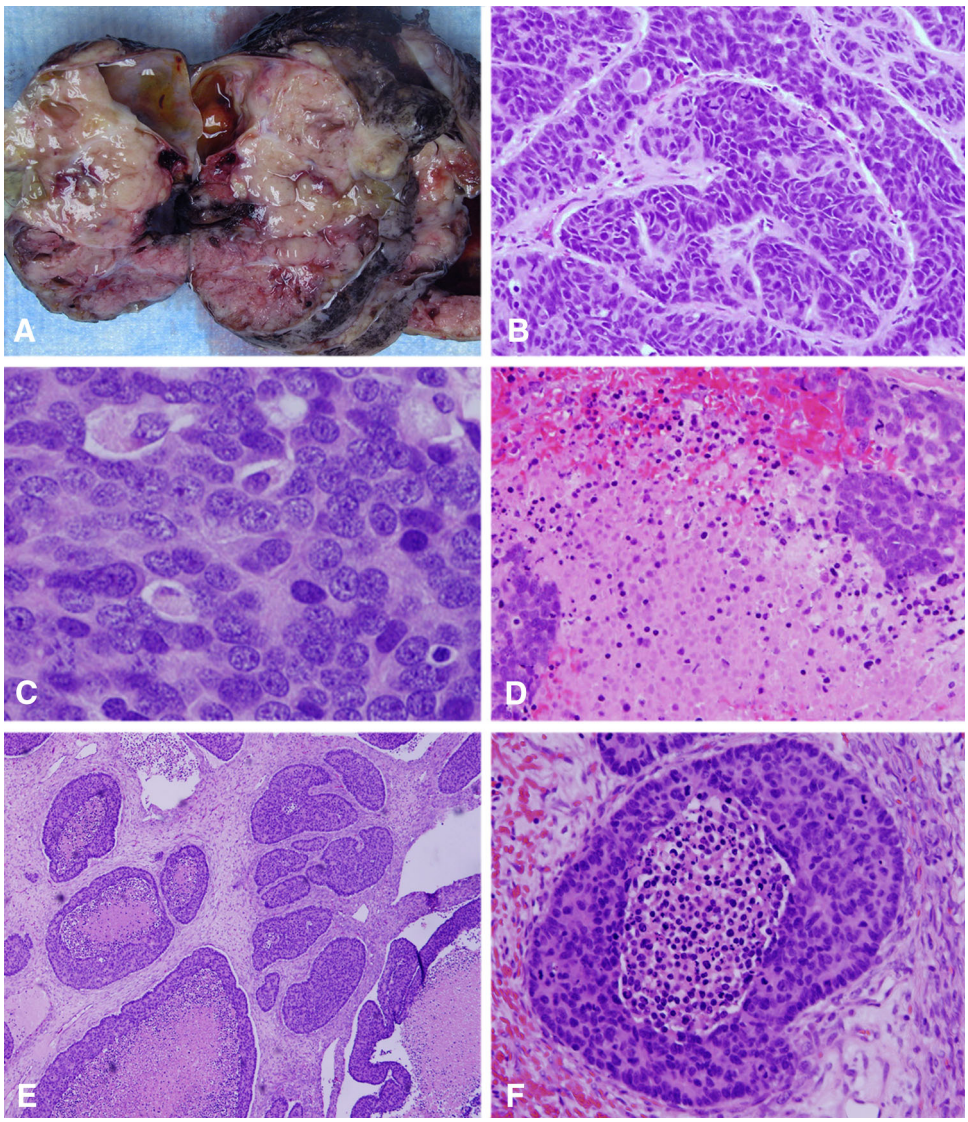

Fig. 3 Gross and microscopic findings of poorly differentiated neuroendocrine carcinoma in the ovary. **a–d** case 3. **a** Gross photo of ovary mass shows a fleshy, tan tumor tissue with focal hemorrhage, necrosis, and cystic change. The tumor also extends to serosa as small nodules. **b–d** Microscopically, the tumor grows as wide trabeculae or as solid sheets with areas of extensive necrosis. The tumor also shows nuclear pleomorphism, high mitotic, and apoptotic figures. **e** and **f** case 4. Microscopic photos reveal numerous large tumor nests with central necrosis. The tumor cells show nuclear pleomorphism and high mitotic figures

heterogeneity in terms of histogenesis and site of origin. In general, neuroendocrine tumors in the gynecologic system express similar generic neuroendocrine markers and to a certain degree, also share some cytological features.

Well-differentiated neuroendocrine tumors in the ovary are histologically similar to carcinoid/atypical carcinoid tumors in the other organs. However, in the ovaries, carcinoids and atypical carcinoids are often present as a part of the components of a teratoma or "specialized teratoma." In some cases, such as in case 1, the neuroendocrine element may be the only tumor component in the ovary. In a previous study, approximately 14 % of ovarian carcinoid tumors were incidentally identified from pathologic examination of excised ovaries for other reasons [3].

Primary ovarian carcinoid tumors may be subdivided into four categories: insular, trabecular, mucinous, and strumal (trabecular carcinoid mixed with thyroid tissue) [11]. In the literature, insular pattern is reported to be the most common subtype, and one-third of patients with insular carcinoid have presented with carcinoid syndrome before treatment [3]. It was suggested that the clinical symptoms of carcinoid were related to the size of tumor [12]. The prognoses of insular, trabecular, and strumal carcinoid are favorable because these tumors in the ovary are rarely associated with metastasis [13], although adhesion to omentum and intestine may occur when these tumors extend to the serosa. However, notably there are rare case reports described as metastatic carcinoid from ovarian primary [14]. As in other organs, atypical carcinoid is differentiated from carcinoid with slightly increased mitoses but lack of significant nuclear pleomorphism and tumor necrosis.

Some reports have indicated that mucinous subtype of carcinoid can be associated with advance tumor stage,

pelvic spread, and metastasis [15–17]. As described in these reports, mucinous carcinoid may be concurrent with mucinous adenoma or adenocarcinoma (i.e., "carcinoma arising in mucinous carcinoid") or as a minor element of a well-differentiated ovary carcinoma [18].

Primary carcinoid tumors, particularly mucinous carcinoid, must be distinguished from metastatic carcinoid tumor from the vermiform appendix, gastrointestinal tract, and pancreatic-hepatobiliary system. It is important to differentiate primary from metastatic carcinoid because the latter is associated high mortality rate in 5 years [9]. The presence of a teratoma and confinement to a single ovary supports an ovarian origin [19]. New studies suggest that immunohistochemical markers, such as CDX-2, may be useful for distinguishing metastatic from primary [20–22].

In contrast to well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas in the ovary are a group of high grade carcinomas with neuroendocrine features and, in general, are not associated with teratomas. Clinically, these tumors progress rapidly and patients often present with advanced disease at the time of diagnosis and metastases to other organs may be present (i.e., as in case 4). Of note, small cell carcinoma of the ovary used to be classified within the neuroendocrine neoplasm category, but since ovarian small cell carcinoma lacks distinct neuroendocrine differentiation, it is now considered as an independent entity [1].

By histologic examination, poorly differentiated neuroendocrine carcinomas have similar morphologic appearances to those large cell/non-small cell neuroendocrine carcinomas in the lung; however, in contrast to large cell neuroendocrine carcinomas in other organs, ovarian large cell neuroendocrine carcinomas may contain a malignant surface epithelial tumor component (i.e., endometrioid carcinoma, serous, or mucinous papillary carcinoma) [8]. In comparing genetic alterations, recent studies have indicated that neuroendocrine components and epithelial tumor components share similar chromosomal abnormalities in ovarian neuroendocrine carcinomas when both are present [7]. In addition, the neuroendocrine components exhibit more genetic abnormalities than the epithelial components. These results suggest that ovarian neuroendocrine carcinomas and ovarian epithelial malignancies share a similar origin and that neuroendocrine carcinomas as a component of the latter become more dedifferentiated and acquire additional genetic abnormalities during tumor differentiation.

Several biomarkers have been used for the diagnosis and follow-up of patients with neuroendocrine tumors. Urine 5-HIAA and serum chromogranin A are relatively specific markers for carcinoid tumor. Others such as pancreatic polypeptide, neuron-specific enolase, and subunit of glycoprotein hormones have been used for screening purposes in patients with tumor syndromes related to hormone secretion. In the histologic evaluation of neuroendocrine tumors, immunohistochemical stains for CD56, synaptophysin, and chromogranin are often used as ancillary studies to confirm neuroendocrine differentiation. In poorly differentiated neuroendocrine carcinomas, reactions for these markers may be weak or even absent. Therefore, simultaneous application of multiple markers is often needed. Additionally, because CD56 is also positive in ovarian sex cord-stromal tumors [23], confirmation of neuroendocrine differentiation requires focal or diffuse positivity for an alternate neuroendocrine marker (i.e., either synaptophysin or chromogranin) in pathologic diagnosis. In recent years, a number of new molecular markers and diagnostic tests including microRNA's and gene transcript PCR analysis have been investigated for their use in early detection and prediction of tumor aggressiveness. However, most of these studies have been based on pancreatic and gastrointestinal neuroendocrine neoplasms, and their diagnostic value for ovarian neuroendocrine tumors needs further study.

In general, the clinical management of ovarian neuroendocrine neoplasms is surgical resection with the goal of attaining negative margins. For poorly differentiated neuroendocrine carcinoma, general consensus for optimal treatment has not yet emerged. Nevertheless, post-operative radiation and chemotherapy are often applied as an optional treatment.

In conclusion, ovarian neuroendocrine tumors consist of a group of heterogeneous malignancies that express similar cellular immunohistochemical markers. This group of tumors can be divided into carcinoid/atypical carcinoid and large cell neuroendocrine carcinoma. New studies indicate that these two groups of tumors have different histogenesis. In the ovary, neuroendocrine tumor morphology, biologic behavior, and clinical prognosis are closely related to histogenesis and site of origin.

Compliance with ethical standards

Conflict of interest None.

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