

Histological Origin and Clinicopathological Analysis of Primary Ovarian Neuroendocrine Neoplasms

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Abstract

Purpose

To investigate the histological origin and clinical and pathological features of primary ovarian neuroendocrine neoplasms.

Methods

We retrospectively analyzed nine cases of ovarian neuroendocrine neoplasms diagnosed at our hospital from January 2009 to January 2021.

Results

The mean age of the nine patients was 44.9 ± 15.2 years (range, 28–68 years). Six cases manifested ovarian carcinoid cancer, and the pathological types were insular and trabecular carcinoid; microscopic observation showed that the carcinoid components were limited and that stromal reaction was slight. Four cases showed teratomas, with the carcinoid components not displaying adjacent mucinous glands; and the other cases exhibited carcinoid cancer as the only tumor component, without adjacent or migratory epithelial components. The six patients were followed up for 76.6 ± 41.2 (6–123) months after resection, without disease. Two cases manifested adenocarcinoma admixed with neuroendocrine carcinoma, and the intermigration of neuroendocrine carcinoma and adenocarcinoma components could be observed; and one case was an isolated small cell neuroendocrine carcinoma with no epithelial proximity or migration observed. Adenocarcinoma admixed with neuroendocrine carcinoma and small-cell neuroendocrine carcinoma exhibited an obviously promoted interstitial reaction and damaging infiltration: these three patients underwent radical surgery supplemented by postoperative radiotherapy and chemotherapy, and follow-up lasted 34.6 ± 24.2 (7–52) months; two patients died and one showed recurrence.

Conclusions

Ovarian neuroendocrine neoplasms may reflect multiple tissue origins, carcinoid and simple neuroendocrine neoplasms with no adjacent, transitional epithelium, and may originate from original/transformed neuroendocrine cells or stem cells of the ovarian stroma. In addition, the adenocarcinoma admixed with neuroendocrine carcinoma may originate from dedifferentiated epithelium. The prognosis with carcinoid cancer is favorable, while the prognosis for neuroendocrine carcinoma is poor.

Introduction

Primary neuroendocrine neoplasms (NENs) in the female reproductive system principally occur in the cervix and rarely in the uterus, ovary, and fallopian tube. The fifth edition of the WHO classification criteria for the female reproductive system describes NENs as including neuroendocrine tumors (NET), neuroendocrine carcinoma (NEC), and carcinoma admixed with neuroendocrine carcinoma (CNEC). Ovarian NEC includes large-cell neuroendocrine carcinoma (LCNEC) and small-cell neuroendocrine carcinoma (SCNEC)[1]. Although ovarian NENs express the same neuroendocrine markers, the clinical manifestations, biological behaviors, and prognoses are quite different [2].

There are various views on the origin of ovarian NEN tissue, and some researchers believe that carcinoid tumors originates from enteric intraepithelial neuroendocrine cells of mature teratomas or from the differentiation of ovarian mesenchymal stem cells, which can be clinically manifested as carcinoid syndrome. Ovarian NECs may originate from ovarian neuroendocrine cells or stem cells, and CNEC is closely related to the epithelium. CNEC may originate from different areas of epithelial cell malignancies or be a dedifferentiated component of epithelial cell carcinoma [3–5], and it is often associated with poor clinical outcomes. It is difficult to execute studies on large samples of primary ovarian NENs, and the relationships among the tissue origins of the tumor components, pathology, and clinical aspects remain worthy of further discussion.

The data from nine cases of primary ovarian NENs at our hospital were retrospectively analyzed, and the possible tissue origins of different types of tumors in NENs were predicted through careful observation of histopathology and immunohistochemistry. The relationships among tissue origin, pathological morphology, and prognoses were also predicted based upon clinical conditions.

Materials And Methods

Nine cases of ovarian neuroendocrine neoplasms diagnosed from surgical specimens between January 2009 and January 2021 were retrieved from our hospital's database, and the clinical and pathological data were extracted. All of the pathological sections were reviewed by two experienced physicians with professional titles of attending physician or above, and three cases were reviewed by higher-tier hospitals. This is an observational study, approval was granted by the Ethics Committee of the local hospital.

The specimens were fixed in 4% neutral formaldehyde, fully sampled, embedded in paraffin, and sectioned at 4 μ m for routine H&E preparation and observation. For immunohistochemistry, we purchased the following reagents: CD56, CgA, syn, SSTR-2, CK5/6, P40, CK20, CK7, villin, CDX-2, SATB2, PAX8, TTF-1, CA125, ER, PR, PCK, Calretinin, α -inhibin, and KI-67 from Beijing Zhongshan Jinqiao Biological Preparation Company. The staining process was completed using a Roche automatic immunohistochemistry apparatus according to the concentrations recommended in the manual. Positive intensities and proportions of cells were observed under a microscope, and negative and positive controls were implemented for all of the tests.

Our diagnoses were based on the 5th Edition of the WHO Classification of Tumours, Female Genital Tumours [1], and the clinical staging was based on the ovarian cancer staging of the International Union of Gynecology and Obstetrics (FIGO) in 2014. We used SPSS v.19.0 statistical software for analysis, and continuous data are expressed as means \pm standard deviation.

Results

Clinical data

The mean age of our nine patients was 44.9 ± 15.2 years (range, 28–68 years). Eight patients exhibited unilateral ovarian masses, and case 4 was complicated by contralateral mature cystic teratoma of the ovary. Of the six cases with ovarian carcinoid tumors, case 3 and case 5 presented with abdominal discomfort and palpable masses, and case 5 self-complained of facial flushing and severe constipation for over seven months; the remaining four cases showed no obvious symptoms, and ovarian masses were found incidentally during physical examination. Three patients with CNEC/NEC presented with abdominal discomfort and abdominal pain, and case 7 presented with irregular postmenopausal bleeding. The nine patients had no family history of genetic diseases within three generations, and no previous history of neuroendocrine tumors at other sites or of gynecological ovarian tumors (Table 1).

Table 1
Clinical demographic characteristics

Cases	Age	gestation	tumor location	Clinical presentation	Teratoma	Imaging studies	Tumor marker	FIGO staging
1	28	G0P0	Left	N/A	Yes	Ultrasound B: Mixed mass in the left ovary, considered teratoma	N/A	ⅡA
2	31	G1P1	Left	N/A	Yes	Ultrasound B: Mixed mass in the left ovary, considered teratoma	N/A	ⅡA
3	36	G2P1	Right	Abdominal mass	Yes	Ultrasound B: Mixed mass in the right ovary, considered as teratoma	N/A	ⅡA
4	29	G0P0	Left	N/A	Yes	Ultrasound B: Mixed mass in the left ovary, considered as teratomas	N/A	ⅡA
5	48	G1P1	Left	Abdominal mass, astringtion, flushing	No	CT Scan: A soft tissue density mass with a maximum diameter of 7.5cm in the left adjunct area, a clear margin and homogeneous parenchyma density	N/A	ⅡA
6	54	G3P1	Right	N/A	No	Ultrasound B: A 5.0cm area of low echo in the right ovary, clear boundary and uneven internal echo, considered as fibroma	CEA	ⅡA
7	68	G3P2	Right	Abdominal pain, mass Vagina bleeding	No	CT Scan: A 18.8cm mixed echo area in the upper part of the uterus, non-echo area in the solid part, considered as cystadenocarcinoma	CA125	ⅡA
8	65	G2P2	Left	Abdominal pain, abdominal mass	No	CT Scan: A 14.5cm cystic solid lesion with mural nodules in the anterior left side of the uterus, considered as a malignant tumor	AFP, CEA	ⅢC
9	45	G1P1	Right	Abdominal pain, abdominal mass	No	CT Scan: Irregular mixed signals of 10.0cm shape in the right pelvic cavity, considered as ovarian malignant tumor	CA125	ⅢC
N/A: Not Applicable								

All of the patients complied with serum tumor-marker examination preoperatively, and CEA (13.26 ng/ml) was slightly elevated in only one of the six carcinoid cases. CA125 elevated in all three cases of CNEC/NEC (range, 37.6–161 U/ml), but AFP (75.54 ng/ml) and CEA (56.71 ng/ml) were elevated in one case respectively. Prior to surgery, nine patients each underwent a B-ultrasonographic examination, of whom four patients underwent a CT examination. Six patients were considered to have carcinoid cancer in the form of a teratoma or ovarian fibroma, and three patients with CNEC/NEC were suspected to have a malignant ovarian tumor that was posited to be an adenocarcinoma. Clinical staging of the six cases of ovarian carcinoid revealed one case of NEC at stage IA, and two cases (cases 8 and 9) of CNEC at stage IC (cancer cells were found in the abdominal rinses) (Table 1).

Pathologic Findings

Grossly, we observed six cases of carcinoid tumor with an average maximal diameter of 5.8 cm (3.5–8.0 cm), and the tumor surface was smooth and intact. Four cases showed typical teratomatous morphology, with oil, hair, and a solid and tough area; the other two teratomas were rough and exhibited no definite necrosis. Two cases were of CNEC, with a maximal diameter of 12.5 cm and 17.0 cm, respectively. One case showed SCNEC, with a maximal diameter of 14.0 cm. The CNEC and SCNEC tumors were solid cysts, brittle, necrotic, and adhered to surrounding tissues.

Microscopic observations showed that all six cases of carcinoid tumor were confined to the ovary, with a mild interstitial reaction and no definite necrosis; there were abundant thin-walled capillaries around the tumor, and the cellular morphology was mild, the chromatin fine, and the nucleoli were not obvious—the mitotic image was $< 2/2 \text{ mm}^2$. Of the cases, five showed insular carcinoid, and four cases manifested teratomas. With respect to the latter, the scope of the tumor lesion was small, and there was no juxtaposition between tumor components and glandular components in the teratoma under light microscopy. The remaining case was of trabecular carcinoid, with an oval nucleus arranged perpendicular to the long axis of the trabecular cable, and locally resembled a pseudoadenoid structure; no other tumor components were observed, and there was no adjacency or migration with ovarian epithelium. All three cases of CNEC/NEC exhibited obvious necrosis, damaging growth, and local invasion of the ovarian capsule; cell morphology was diverse, the chromatin was rough, and the cells were mitotically active. Two of these were CNECs, indicating a mutual transition of the two components; the other one was SCNEC and manifested no clearly observed migration with epithelial components.

Regarding immunohistochemical analysis, neuroendocrine markers (CD56, CgA, syn, and SSTR2) were expressed in six carcinoid patients to varying degrees. The positive staining of the broad-spectrum epithelial marker PCK was less intense than that of the glandular epithelium, and staining for Ki-67 was $< 3\%$. CD56, CgA, syn, and PCK were expressed to different degrees in three SCNEC/CNEC patients, but SSTR2 was not expressed; TTF1 was positive in patients with SCNEC. Other indices such as calretinin, α -inhibin, SATB2, PAX8, ER, and PR were negative (Table 2, Figure 1).

Table 2
Pathological features of neuroendocrine neoplasms

Cases	Maximum mass (cm)	Lesion range (cm)	Pathologic types	With cancer	Distribution characteristics	Stromal reaction	Capsule invasion	Vascular invasion	Immunohistochemistry positive	Pathologic findings
1	6.0	2.0	Insular	N/A	No adjacent mucous glands	Not obvious	N/A	N/A	CgA \square SyN \square CD56 \square SSTR2 \square CDX2	WDNT
2	5.5	0.8	Insular	N/A	No adjacent mucous glands	Not obvious	N/A	N/A	CgA \square SyN \square CD56 \square SSTR2 \square CDX2	WDNT
3	6.5	1.2	Insular	N/A	No adjacent mucous glands	Not obvious	N/A	N/A	CgA \square SyN \square CD56 \square SSTR2 \square CDX2	WDNT
4	3.5	0.5	Insular	N/A	No adjacent mucous glands	Not obvious	N/A	N/A	CgA \square SyN \square CD56 \square SSTR2 \square CDX2	WDNT
5	8.0	2.0	Insular	N/A	Exist independently	Not obvious	N/A	N/A	CgA \square SyN \square CD56	WDNT
6	5.5	4.0	Trabecular	N/A	Exist independently	Visible	N/A	N/A	CgA \square SyN \square CD56 \square SSTR2	WDNT
7	14.0	diffuse	LCNEC	Adenocarcinoma	Mixed distribution	Damage	Yes	Yes	CgA \square SyN	PDNC
8	9.5	diffuse	LCNEC	Adenocarcinoma	Mixed distribution	Damage	Yes	Yes	CgA \square CD56	PDNC
9	20.0	diffuse	SCNEC	N/A	Exist independently	Damage	Yes	Yes	CgA \square CD56	PDNC

WDNT well-differentiated neuroendocrine tumor, PDNC poorly differentiate neuroendocrine carcinoma, N/A: Not Applicable

Treatment And Clinical Follow-up

All of the patients were treated surgically. For the six cases with carcinoid three patients underwent simple cyst stripping, one underwent unilateral adnexectomy and contralateral ovarian cyst stripping; and two underwent hysterectomy and affected adnexectomy, without adjuvant chemoradiotherapy. Three patients with CNEC/NEC underwent total uterine, bilateral adnexal, and pelvic lymph-node resection and partial omentectomy; and they received platinum-based combined chemotherapy and radiotherapy after surgery. All of the patients were closely followed up (Table 3).

The follow-up period was 76.6 ± 41.2 (6–123) months from the date of diagnosis to July 2021, and all six patients with carcinoid cancer survived without disease. Recurrence or death occurred in three patients with CNEC/NEC, and follow-up lasted 34.6 ± 24.2 (7–52) months: two patient died and one case had a recurrence. Case 7 had liver metastasis 39 months postoperatively, and neuroendocrine carcinoma was diagnosed by liver biopsy. Case 8 developed cancerous ascites six months postoperatively, and ascites cytology suggested adenocarcinoma and neuroendocrine carcinoma; the patient died seven months after the operation. Case 9 exhibited pelvic metastasis and rectal invasion 44 months after surgery, and died 52 months after surgery (Table 3).

Table 3 Clinical treatment and follow-up

Cases	Operation method	Chemotherapy	Follow-up (status, month)
1	Cyst removal	N/A	Disease-free survival 58
2	Cyst removal	N/A	Disease-free survival 104
3	Cyst removal	N/A	Disease-free survival 123
4	Unilateral salpingo-oophorectomy(left), cyst removal(right)	N/A	Disease-free survival 6
5	Total hysterectomy, unilateral salpingo-oophorectomy(left)	N/A	Disease-free survival 92
6	Total hysterectomy, unilateral salpingo-oophorectomy(left)	N/A	Disease-free survival 77
7	Total hysterectomy, salpingo-oophorectomy, pelvic lymph node and omentum resection	Yes	recurrence 45
8	Total hysterectomy, salpingo-oophorectomy, pelvic lymph node and omentum resection	Yes	death 7
9	Total hysterectomy, salpingo-oophorectomy, pelvic lymph node and omentum resection	Yes	death 52

N/A: Not Applicable

Discussion

Ovarian NENs are rare, accounting for only 0.5–1.7% of total body NENs and approximately 0.1% of malignant ovarian tumors [6]. Ovarian NET is primarily carcinoid and often closely related to teratomas. Atypical carcinoid tumors and high-grade NETs are seldom reported. Simple NEC is rare and often associated with adenocarcinoma so as to develop into CNEC, and offers a poor clinical prognosis. In the present study, we noted the clinicopathological features of nine cases of NENs, speculated the possible tissue origin of different tumor types, and analyzed the relationship between biological behavior and clinical prognoses for different pathological types.

Most ovarian carcinoid cancer is revealed to be teratoma. Some researchers have recognized that the core particles of carcinoid tumor in teratomas were consistent with neuroendocrine particles in the foregut and hindgut using electron microscopy, and they speculated that ovarian carcinoid in teratomas may originate from neuroendocrine cells in the intestinal epithelium[1]. However, in our study, we noted no carcinoid elements in the teratomas that were adjacent to or migrated to myxoid glands, and the morphology did not support the origin as intestinal intraepithelial neuroendocrine cells. It is also posited that neuroendocrine differentiation of primitive ovarian stem cells or scattered ovarian neuroendocrine cells are possible tissue sources of NENs[3, 7–9], and that activation of accompanying gene sequences from non-neuroendocrine cells in the ovary can also be transformed into neuroendocrine tumors[4, 5]. These two views may explain the tissue origin of the neuroendocrine tumor as the sole tumor component, but it is difficult to explain the mixed presence of NECs and epithelial carcinoma. In our investigation, two cases (cases 5 and 6) of simple carcinoid and SCNEC (case 9) manifested a neuroendocrine tumor as the only tumor component, without proximity or migration to other epithelial components. According to the tissue morphology, we speculated that the original/transformed neuroendocrine cells or stem cells in the ovarian interstitium were derived.

Compared with NECs in other organs, ovarian NEC is often associated with epithelial tumors[10], and it is presumed that ovarian NEC with adenocarcinoma may be caused by different directions of differentiation taken by glandular epithelium or stem cells[4, 5]. Gene amplification and deletion of NEC components and adenocarcinoma were compared using whole-genome sequencing, showing that NEC components bore more genetic changes than did adenocarcinoma, suggesting that NEC components may be a dedifferentiated component of adenocarcinoma; and these authors demonstrated that NEC combined with adenocarcinoma behaves more aggressively than normal adenocarcinoma[11]. We observed intermigration between NEC and adenocarcinoma components in cases 7 and 8, and inferred from the morphology that neuroendocrine carcinoma is a dedifferentiated component of adenocarcinoma.

Although the pathological features of ovarian NENs are obvious, the preoperative clinical, imaging, and laboratory features are not specific. Ovarian carcinoid tumors are small in size, with limited lesions and no clear necrosis or invasion. Imaging and tumor markers provide no clear suggestive effect, and the majority of the tumors are found unintentionally [12]. Even pathological examination may ignore very small lesions, and only one-third of ovarian insular carcinoid cancers are associated with carcinoid syndrome[13, 14]. Of the 6 cases of carcinoid in this group, only two cases manifested an abdominal mass and manifested carcinoid syndrome; and only one patient exhibited tumor markers and a slight elevation in CEA, with malignancy not considered upon imaging. However, CNEC/NEC is generally associated with a large mass accompanied by necrosis and cystic changes; and there are abdominal symptoms and abnormal tumor markers, making the preoperative diagnosis of malignant tumor relatively straightforward. However, neuroendocrine carcinoma is often unclear. In our study, tumor markers in three patients with SCNEC/CNEC were all abnormally elevated; and although imaging was consistent with a diagnosis of malignancy, there was no suggestive diagnosis of neuroendocrine components. It is therefore difficult to make a definitive diagnosis of ovarian NENs prior to surgery, and thus vigilance should be observed in the pathological diagnosis—particularly when clinical symptoms related to carcinoid syndrome exist, and sufficient samples should also be carefully examined. Patients with ovarian adenocarcinoma should be carefully observed for the presence of NEC components, as NEC often predicts a worse prognosis[11].

Accurate diagnosis of primary ovarian NENs is very important for the formulation of a treatment plan; and ovarian NENs should be distinguished from metastatic NENs, adenocarcinoma, granulocytomas, and Sertoli cell and other common tumors. In addition, different directions of differentiation originating from the appendix should be excluded. Medical history, observation of tumor distribution, and the rational use of immunohistochemistry allow clinicians to identify relevant clinical history; and whether there is involvement of bilateral ovarian or multiple sites, or of vascular involvement or other supporting metastases. The primary disease is usually unilateral and confined to the ovary, with a teratomatous background or mixed with adenocarcinoma[15]. Functional imaging with SSTR is also an important modality used to determine the source of NENs, and it can be applied to disease staging, preoperative

imaging evaluation, and disease re-staging[16]. NENs express neuroendocrine and epithelial markers, and negative staining for PAS in mucus allows discrimination from adenocarcinoma. None of the patients in our group exhibited any history related to other aspects, and the pathological morphology and immunohistochemistry all supported the tumors as primary ovarian NENs.

The clinical features and prognosis of ovarian NENs are related to pathological types. Ovarian carcinoids, island carcinoids, beam carcinoids, and thyroid-type carcinoids are usually small, rarely associated with metastasis, augur an acceptable prognosis [12], and the 10-year survival rate of stage I patients after surgery nears 100%[17]. Mucinous carcinoids may be a companion component of well-differentiated ovarian cancer, they and can be associated with metastasis and advanced tumor stage [18, 19]. Compared with carcinoid tumor, ovarian CNEC/NEC is generally characterized by a large size and rapid progression; and patients are often diagnosed with advanced disease, which may be transferred to other organs[4]. Even in stage I, the prognosis remains very poor, and multivariate analysis showed that possessing a high proportion of neuroendocrine components was an independent risk factor for poor prognosis [20]. Although in our study six cases of carcinoid were small in size and revealed no invasion of the ovarian capsule or vessels, most ovarian carcinoids follow an indolent clinical course. In addition, there are few reports of advanced stages[6, 21], and thus early surgery and long-term postoperative follow-up remain necessary. Three patients with CNEC/SCNEC relapsed, showed metastases, or died despite more extensive and radical surgery and postoperative adjuvant chemoradiotherapy. Pathological examination of our patients' recurrent and metastatic components showed that neuroendocrine carcinoma was associated with a greater tendency for metastasis and recurrence relative to the adenocarcinoma that accompanies it.

In conclusion, primary ovarian NENs constitute a group of highly heterogeneous tumors whose tissue origin may be multi-pathway. Carcinoid and simple NEC may originate from original/transformed neuroendocrine cells or stem cells in the ovarian stroma, while the neuroendocrine component of CNEC may originate via dedifferentiation of adenocarcinoma. There are significant differences in biological behavior and prognosis among different pathological types, with carcinoid showing a satisfactory prognosis, while CNEC/NEC portends a poor prognosis. Due to the rarity of NENs in the ovary, the cases in this study were limited; and further investigation of the exact tissue source and the generation of clinical prognoses of some rare pathological types are required.

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Declarations

Conflict of interest

The authors declare that they have no conflicts of interest.

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Competing Interests

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Author Contribution

Yuxiang Shi: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

Li Li: Data collection or management

Zheng Huang: Data analysis

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Figures

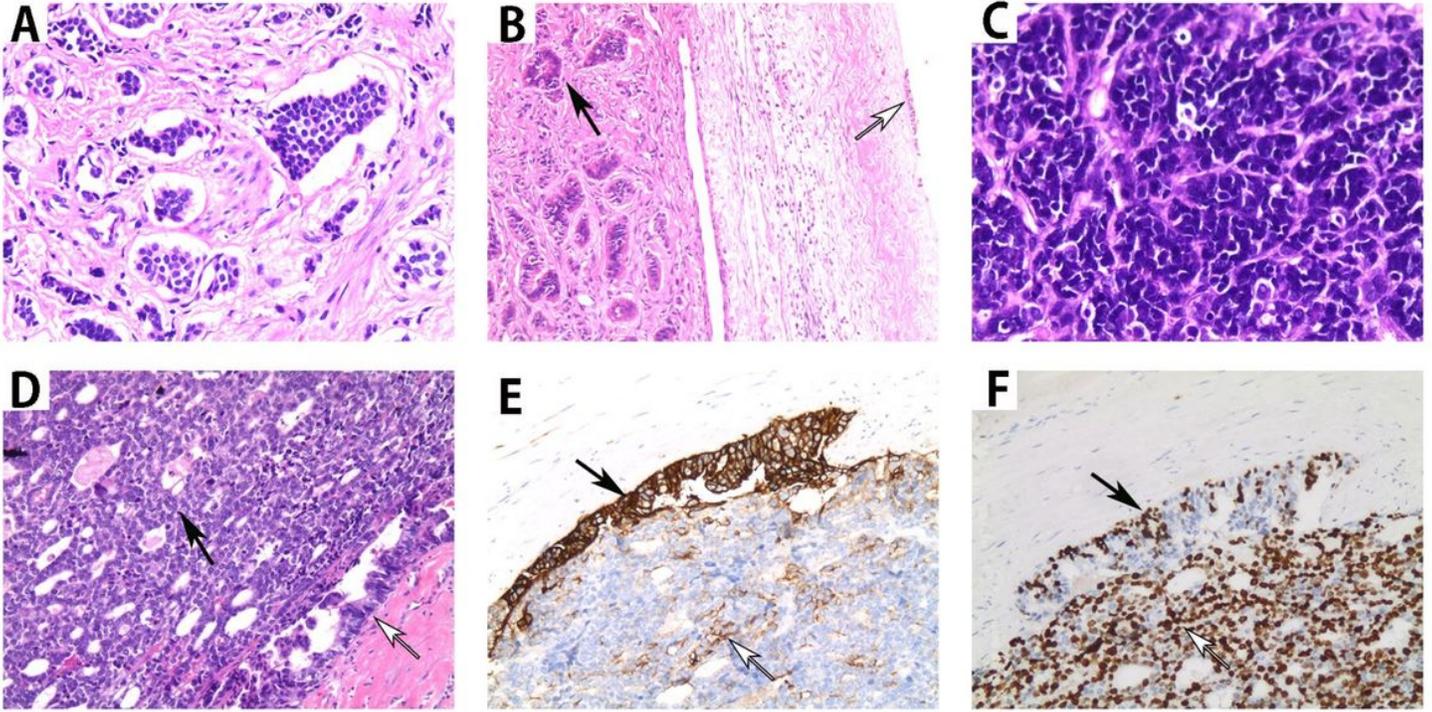


Figure 1

a Insular carcinoid: mild cell morphology, no obvious stromal stimulating reaction, and no adjacent glandular epithelium around the tumor. b Trabecular carcinoid: no destructive infiltration and necrosis (↑), no migration with ovarian surface epithelium (⇑) . c Small cell neuroendocrine carcinoma: obviously nuclear atypia, sparse cytoplasm, diffuse tumor growth and single tumor component. d Adenocarcinoma admixed with neuroendocrine carcinoma: large cell neuroendocrine carcinoma (↑) is uniform, with an ovoid nucleus, and migrates with abundant adenocarcinoma components in cytoplasm (⇑). e Immunohistochemistry of PCK: large cell neuroendocrine carcinoma was mottled with varying degrees of positivity (↑), whereas adenocarcinoma component (⇑) was diffusely cytoplasmic with strong positivity, and intermigration of the two was observed. f Immunohistochemistry of KI-67: large cell neuroendocrine carcinoma component (↑) has high proliferative activity, while adenocarcinoma component (⇑) is relatively low.