Ovarian Neuroendocrine Tumors: a Single-institution Experience

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Abstract

Background: Ovarian neuroendocrine tumors (O-NETs) are uncommon malignant carcinomas with a poor prognosis. There are no standardized practice guidelines as impacted by the lack of sufficient data regarding the clinicopathologic features and management of O-NETs. This study aimed to analyze the clinical manifestations, diagnosis and treatment of O-NETs.

Methods: We retrospectively analyzed ten cases with ONETs admitted to the Department of Gynecology of the First Affiliated Hospital of Zhengzhou University from August, 2015 to May, 2020.

Results: The median age of cases at diagnosis was 38.4 years (from 20 to 58). The most common presentation was abdominal pain (4/10), followed by pelvic mass (3/10), and vaginal bleeding (1/10). Two cases had no symptoms. All cases underwent the surgery. The diagnosis was confirmed by the postoperative histopathology. Tumors expressed at least one neuroendocrine marker (e.g., CD56, chromogranin-A, synaptophysin, or neuron specific enolase). By complying with the International Federation of Gynecology and Obstetrics (FIGO) staging system (2014), three cases were stage I tumors, one case was stage II tumor, and six cases were stage III tumors. Eight cases only received chemotherapy postoperatively, one was administrated with olaparib maintenance after chemotherapy, and one received the chemotherapy followed by the radiotherapy. The follow-up time for cases raged from 10 to 48 months. Two cases died of disease recurrence, while the other 8 cases were in the follow-up. Six cases experienced tumor recurrence.

Conclusion: O-NETs were characterized by high malignancy, low incidence and poor prognosis. The histopathological analysis was considered the gold standard for diagnosis. Surgical resection might be the first choice of therapy, and adjuvant chemotherapy and possible radiotherapy might prolong the survival of some cases.

Background

The existing research on ovarian cancer primarily focused on epithelial ovarian tumors (e.g., serous cancer mucinous cancer, endometrial carcinoma, as well as clear cell carcinoma). However, the research on other rare types (e.g., carcinosarcoma, squamous cell carcinoma and ONETs) has been rare, and it is difficult to achieve a standardized and appropriate clinical management. Primary ONETs refer to uncommon malignant carcinomas with strong invasiveness and poor prognosis, taking up less than 1–2% of ovarian malignant tumors[1]. Most cases are diagnosed with advanced-stage diseases[2]. The histological classification of ONETs consists of 4 categories: atypical carcinoid, typical carcinoid, large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma of the ovary (SCCO)[3]. The histogenesis of ovarian NETs is unknown, and the mentioned tumors are generally mixed with other histological subtypes (e.g., mucinous adenocarcinoma, endometrioid adenocarcinoma or teratoma), which can cause mis diagnosis clinically[4, 5]. Besides, the mentioned tumors express similar neuroendocrine makers (e.g., synaptophysin and chromogranin), so they are grouped together[5]. As

impacted by the low incidence of ovarian NETs, there are only limited studies to guide clinical decisions, thereby imposing great challenges to clinical diagnoses and treatments.

This study presented 10 cases with ONETs treated at the First Affiliated Hospital of Zhengzhou University from 2015 to 2020. Their clinical data were investigated to provide be referenced for subsequent diagnoses and treatments.

Results

Ten cases with O-NETs were identified and included in this study. The incidence of ONETs reached 0.49% (10/2048)of ovarian malignant tumors in our hospital. The clinical features are listed in Table 1. The mean age at diagnosis was 38.4 years (range 20 to 58 years). All cases had no family history of ovarian cancer. The most common presenting symptoms were abdominal pain (4 of 10) or a pelvic mass (3 of 10). Two cases had no symptoms. Only one case presented vaginal bleeding. Preoperative cancer antigen 125 (CA-125, normal range ≤ 35U/ml) levels increases in eight of ten cases. NSE levels slightly increased in two cases. The mentioned tumor markers returned to normal levels after the treatment. All cases underwent ultrasound (US) and computed tomography (CT) before the surgery. As indicated from the US test, the boundary of the mass was unclear, the shape was irregular, and there was abundant blood flow. 6 cases had ascites of varying degrees. The contrast enhanced CT displayed a soft tissue mass with heterogeneous density in the pelvic cavity. No tumoral lesions were identified in the gastrointestinal tract, pancreas-hepatobiliary system or lungs on imaging scan. Furthermore, no image evidenced lymph node metastasis.

The average size of the ovarian tumor was 9.2cm (ranged 4 to 20cm). The tumor was unilateral in 4 cases, and 6 cases were bilateral. In addition, the cut surface of the tumor was gray-white or gray-yellow. Moreover, cystic degeneration, hemorrhage or necrosis were observed. Microscopically, the tumor cells were round or oval, with abundant cytoplasm, prominent nucleoli, as well as active nuclear division. The immunohistochemical results are listed in Table 2.

Table 1
Clinical characteristics of 10 cases with O-NETs

Case	Age(years)	Symptom	Size(cm)	Stage	CA125(U/ml)	Operation
1	20	Mass	20	IC	401.2	BSO
2	26	Pain	5	IIIC	150.7	OB
3	31	Mass	10	IIIC	61.25	TAH/BSO/Om/LN
4	32	Pain	10	IIIC	146.6	TAH/BSO/Om/LN
5	54	Pain	5	IIIB	170.6	TAH/BSO/Om/LN
6	46	Mass	13	IIIC	191.0	TAH/BSO/Om/LN
7	29	N	8	IA	17.95	USO
8	37	N	8	IA	42.13	TAH/BSO/Om/LN
9	51	Pain	8	IIA	120	TAH/BSO/Om/LN
10	58	Bleeding	4	IIIC	14.5	TAH/BSO/Om/LN

CA125: Cancer antigen 125; BSO: Bilateral salpingo-oophorectomy; USO: Unilateral salpingo-oophorectomy; OB: Omental biopsy; TAH: Total abdominal hysterectomy; Om: Omentectomy; LN: Lymph node dissection.

For neuroendocrine components, the tumor cells were positive for CD56 (9/9), Syn (6/8), as well as Cg-A (5/7). In addition, several cases were positive for cytokeratin, PAX-8 and EMA. By complying with the staging standard of the FIGO 2014, two cases were stage IA, one case was stage IC, one case was stage IIA, one case was stage IIIB, and five cases were stage IIIC disease.

All cases underwent the surgery. Two young cases had fertility requirements and were reluctant to undergo the comprehensive operation. Lastly, one case underwent the unilateral salpingo-oophorectomy (USO), the other underwent the bilateral salpingo-oophorectomy (BSO), omentectomy and lymph node dissection. Seven cases underwent the debulking surgery, which consisted of hysterectomy, BSO, lymph node dissection, lymph nodes dissection, omentectomy, and debulking of extra-ovarian cancer. One case with stage IA underwent staging surgery.

Table 2
immunohistochemical results of 10 cases with ONETs

Case	Immunohistochemistry	Diagnosis
1	CD56(+), Syn (+), Cg-A (focal +), Ki-67(70%), Inhibin-a (-), EMA (+), WT-1(-), PAX-8 (±), TTF-1(-)	SCCO
2	CD56(+), Syn (+), Cg-A (-), SMA (-), CD99(-), WT-1(-), KI-67(70%), Vimentin (+), PAX-8(-), CK (+), CK8/18(+)	SCCO
3	CD56(+), Syn (-), NSE (-), EMA (+), FLI-1(-), CD99(-), CD10(+), WT-1(-), ER (-), PR (±), Ki-67(90%), CK (+)	SCCO
4	CD56(+), Syn (-), NSE (-), AE1/AE3(-), FLI-1(±), CD99(+), Inhibi-a (-), Ki-67(40%), CK7(-)	SCCO
5	CD56(focal +), Syn (+), Cg-A (focal +), CK7(+), PAX-8(+), CDX-2(-), WT-1(-), Ki-67(70%), P53(+), CK20(+)	LCNEC
6	CD56(+), Syn (+), Cg-A (+), CK8/18(+), EMA (-), TTF-1(-), PAX-8(-), CK (+), Inhibi-a (-), Ki-67(90%), CK (+)	LCNEC
7	CD56(+), Syn (+), Cg-A(focal+), Inhibi-a (-), AE1/AE3(+), WT-1(-), TTF-1(-), PAX-8(-), Ki-67(70%), EMA (+)	SCCO
8	CD56(+), Syn (+), Cg-A (+), CK (+), PAX-8(+), TTF-1(-), WT-1(-), P40(-), CK7(-), Ki-67(80%), EMA (+)	SCCO
9	Unclear	SCCO
10	CD56(+), Cg-A (-), PAX-8(-), P53(-), CK7(+), AE1/AE3(+), CD34(-), Ki-67(80%), ER (-), PR (-)	LCNEC

LCNEC: Large cell neuroendocrine carcinoma; SCCO: Small cell carcinoma of the ovary

Table 3
Adjuvant chemotherapy regimens and follow-up.

Case	Chemotherapy	Recurrence/Months	Follow-up(months)
1	EP	Y/12	24
2	TC	Y/4	10, DOD
3	EP	N	24
4	TP	Y/6	17
5	TP	Y/5	14
6	TP/Olaparib	Y/4	20
7	EP	Y/5	10, DOD
8	EP	Y/2	12
9	EP	N	27
10	TP /radiotherapy	N	48

EP: Etoposide/Cisplatin; TC: Paclitaxel/Carboplatin; TP: Paclitaxel/ Cisplatin; Y: Yes; N: No; DOD: Dead of disease.

Each case was assessed for their performance status prior to the chemotherapy. Ten cases were ECOG 0–1. The main chemotherapy regimens employed as the adjuvant therapy are listed in Table 3. Five cases treated with EP, and three of them recurred (2, 5, 12 months). Five cases received TP or TC, and four of them relapsed (4, 4, 5, 6 months). Among five cases receiving paclitaxel and platinum, one case was detected with BRCA2 gene mutation administrated with Olaparib after the end of chemotherapy, whereas this case recurred after 4 months. One case received the chemotherapy followed by the radiotherapy. The case was followed up for 48 years, and it was not evidenced that the tumor has recurred. The time from surgery to initiation of chemotherapy ranged from 2 to 4 weeks.

The follow-up time for the ten cases ranged from 10 to 48 months. Two cases died of disease, while the other 8 cases were still in the follow-up. Seven cases recurred after the end of the treatment, and the time reached 2, 4, 4, 5, 5, 6 and 12 months. The sites comprised liver, bones, pelvis, and inguinal lymph nodes. Serum CA-125 increased in three cases during the recurrence.

Discussion

The incidence of ONETs is extremely low, and the result here complied with the fact of 0.49%. The cases were largely in productive ages with the mean age of 38.4 years. As reported by existing studies have reported that ovarian neuroendocrine carcinoma could also occur after menopause[6, 7]. Abdominal pain

and pelvic mass refer to the main symptoms, complying the findings of existing studies, which suggested the mentioned tumors lack specific clinical manifestations. Cases have no symptoms at the early stage of the disease. Like other ovarian malignant tumors, early detection is difficult. O-NETs are progressively solid and cystic, bilateral, and large. Most cases (6/10) presented advanced-stage diseases during the diagnosis, which was consistent with the literature[2]. It was therefore suggested the tumors have an aggressive clinical behavior with a high tendency to metastasize distant organs. However, none of the cases had retroperitoneal lymph node metastasis, which seemed to imply a low rate of lymph node metastasis in O-NETs. The rate of lymph node metastasis has been rarely reported in the published literature.

On the whole, US and CT usually lack specific findings in ONETs cases. A research suggested that different morphological features on the magnetic resonance imaging (MRI) may indicate the mentioned rare malignant tumors[8]. However, it is insufficient to make a diagnosis by imaging test alone[9]. In this study, serum CA-125 levels increased in most cases (8/10) during the diagnosis. It seemed to indicate a link between CA-125 and these tumors. Existing studies confirmed that CA-125 level is closely related to epithelial ovarian cancers and can be exploited for the monitoring and diagnosis of epithelial ovarian cancers[10, 11]. Accordingly, further studies are required to analyze the relationship between CA-125 and ONETs. Ascitic fluid cytology was also performed, and only two cases found malignant cells in ascites or peritoneal lavage fluid, which demonstrated that it may be difficult to identify malignant cells derived from O-NETs in ascitic fluid. Thus, histopathological analysis of tissue specimens is critical to the diagnosis of O-NETs.

While most ONETs can be recognized on H□E staining, immunohistochemistry is required to confirmed the diagnosis[4]. The results of immunohistochemistry showed tumors expressed at least one neuroendocrine marker (e.g., Cg-A, CD56 or Syn). The mentioned markers have been applied in practices[12, 13]. In this study, CD56 was suggested as the most sensitive marker to demonstrate the neuroendocrine nature of the mentioned tumors, and it was expressed in all cases. However, CD56 lacked specificity since it was also expressed by nonendocrine tissues (e.g., renal tubules, ovarian sex cord-stromal, and thyroid follicular cells)[14–16]. For this reason, some authors did not recommend the use of CD56 alone to demonstrate neuroendocrine components[12, 14]. Syn seem to be more sensitive than Cg-A. According to the cases of this study, Syn was either wore widely expressed than Cg-A or was positive when Cg-A was negative. Besides, some cases expressed cytokeratin, which might help to confirm the epithelial nature of the tumors. Given the existing study, immunohistochemical markers could contribute to the differential diagnosis of O-NETs. Organ related markers used for this such as thyroid transcription factor-1 (TTF-1) for the thyroid and lung, islet-1 (ISL-1) for pancreas, PAX-8 for the thyroid, and CDX-2 for the gastrointestinal tract[17].

At present, the primary treatment for ONETs is generally surgical resection with adjuvant chemotherapy, but there is still no standard guideline[18]. Surgical resection aims to obtain negative margins. A recent study indicated that surgeries could significantly improve survival rates, and complete surgical resection should be recommended as the primary modality[7]. In this study, one case accepted the diagnostic

laparoscopy, which suggested that complete primary debulking surgery (PDS) could not be performed. The case received neoadjuvant chemotherapy followed by internal debulking surgery (NACT-IDS). The role of diagnosis laparoscopy for patients with advanced-stage ovarian cancer was reported[19, 20], and the mentioned studies will be help present a similar method for ONETs. Some patients diagnosed with O-NETs are of childbearing ages and willing to undergo fertility-sparing surgery. However, fertility-sparing surgery has been controversial. Small case series have reported patients undergoing USO and adjuvant chemotherapy achieved good results[21, 22]. Another study reported 26 cases undergoing USO, and none of the cases had a subsequent successful pregnancy[23]. In this study, two cases accepted fertility-sparing surgery. One case who underwent BSO relapsed after 5 months of treatment and died 10 months later, and the other case who underwent USO recurred 12 months after the end of the treatment. The result was not ideal. In addition, postoperative chemotherapy may affect their ovarian function. Accordingly, in-depth studies should be conducted to determine whether fertility-sparing surgery is reasonable for patients with ovarian neuroendocrine carcinoma.

Present adjuvant therapies refer to data from pulmonary literature, including chemotherapy and radiation[2]. In this study, 60% of cases (3/5) who treated with EP recurred, and 80% of cases (4/5) who received paclitaxel/platinum relapsed. 50% recurred in 6 months of chemotherapy, which suggested that these tumors might respond poorly to the chemotherapy. Yang et al. reviewed sporadic case reports, and their study failed to confirm survival benefits from chemotherapy[24]. Two cases who received EP have been followed up for 24 and 27 months, without any diseases. The paucity of data revealed that EP chemotherapy may benefit patients. Due to the limited data, the efficacy of the two chemotherapy regimens cannot be statistically analyzed, and there is also no relevant research in the literature. In this study, only one case received the radiation therapy, which might be partly due to the low rate of radiation use to treat ovarian carcinoma histology. The case has been followed up for 48 months, and it was not evidenced that the tumor recurred. The role of radiotherapy in the treatment of O-NETs remains largely unclear, whereas several reports have suggested a potential benefit[25, 26]. Radiotherapy is worth further exploring in O-NETs. At present, there have been few studies on targeted therapy in O-NETs. In this study, one case with BRCA2 germline mutation was maintained with PARP inhibitor (Olaparib). The case was not improved from Olaparib and recurred after 4 months. More cases are required to be recruited to study the role of PARP inhibitors in O-NETs.

Conclusion

In brief, O-NETs are uncommon malignant carcinomas and aggressive disease with poor prognosis. The diagnosis of the mentioned tumors should comply with histopathological analysis of tissue specimens, and immunohistochemistry plays an important role in diagnosis and differential diagnosis. Though large-scale case studies have been rare, this study suggested that surgical resection may be the first choice of therapy, and adjuvant chemotherapy and possible radiotherapy may prolong the survival of some cases. For low incidence, this study recommended to establish a global database to collect and analyze the mentioned data for in-depth studies of its prognosis and therapeutic regimens.

Methods

We retrospectively analyzed ten cases with ONETs admitted to the Department of Gynecology of the First Affiliated Hospital of Zhengzhou University from August, 2015 to May, 2020. Inclusion criteria were cases who were confirmed by postoperative pathology; the exclusion criteria were patients who could be well followed or with incomplete clinical data. The pathologic diagnosis was confirmed by a pathologist who was proficient in gynecologic malignancies and then reviewed by another pathologist. Clinical data were collected (e.g., age, main symptoms, auxiliary examination, FIGO stage, pathology, treatment and prognosis). The follow-up period was defined as the time between the initial diagnosis of ONETs and the last date of contact or death. ECOG score standard was adopted to assess the performance status. Tumors were staged with FIGO staging classification for ovarian carcinomas.

All cases signed the informed consent for surgery before receiving treatment. The present study was a systematic retrospective analysis, which did not affect the treatment. The data collection and analysis were approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

Abbreviations

ONETs: Ovarian neuroendocrine tumors; LCNEC: Large cell neuroendocrine carcinoma; SCCO: Small cell carcinoma of the ovary; FIGO: International Federation of Genecology and Obstetrics; ECOG: Eastern Cooperative Oncology Group; Syn: Synaptophysin; Cg-A: Chromogranin-A; CA125：Cancer antigen 125; TTF-1: thyroid transcription factor-1; ISL-1: islet-1; US: Ultrasonography; CT: Computed tomography; MRI: Magnetic resonance imaging; USO: Unilateral salpingo- oophorectomy; BSO: Bilateral salpingo-oophorectomy; PDS: Primary debulking surgery; IDS: Internal debulking surgery; OB: Omental biopsy; TAH: Total abdominal hysterectomy; Om: Omentectomy; LN: Lymph node dissection; EP: Etoposide/Cisplatin; TC: Paclitaxel/Carboplatin; TP: Paclitaxel/ Cisplatin; DOD: Dead of disease.

Declarations

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Authors' contributions

WZ designed this study and wrote the manuscript. WF, LL and SC participated in collection and analysis of data. MC and LH reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets supporting the conclusion of this article is included within the article.

Ethics approval and consent to participate

All procedures performed in study involving human participants were in accordance with the ethical standards of the Ethics Committee of the First Affiliated Hospital of Zhengzhou University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not application

Competing interests

The authors declare that they have no competing interests.

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