Systematic retrospective analysis of 10 cases of neuroendocrine tumors of the ovary: diagnosis, treatment and follow-up

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Abstract

Background

Neuroendocrine tumors of the ovary are uncommon malignant carcinomas with a poor prognosis. There are no standardized management guidelines because of lack of knowledge about these tumors. The objective of this study is to analyze the clinical manifestations, diagnosis and treatment of ovarian neuroendocrine tumors (ONETs).

Results

Median age at diagnosis was 38.4 years (range 20–58). The main clinical presentations were abdominal pain or a pelvic mass. Two patients underwent fertility-sparing surgery and the others underwent cytoreductive surgery. The finial diagnosis depended on postoperative histopathology. According to the staging standard of the International Federation of Gynecology and Obstetrics (FIGO), three patients had stage I disease, one stage II, and six patients had stage III disease. Eight patients received chemotherapy alone postoperatively, one was maintained with Olaparib after chemotherapy, and one received chemotherapy followed by radiotherapy. The follow-up time for patients raged from 10 to 48 months. One patient died, while the other 9 patients were in follow-up. Seven patients experienced tumor recurrence.

Conclusion

Ovarian neuroendocrine tumors are characterized by high malignancy, low incidence and poor prognosis. Histopathological analysis is considered the gold standard for diagnosis. Surgical resection may be the first choice of therapy, and adjuvant chemotherapy and possible radiotherapy may prolong the survival of some patients.

Background

At present, the research on ovarian cancer mainly focuses on epithelial ovarian tumors such as serous cancer mucinous cancer, endometrial carcinoma, and clear cell carcinoma. However, the research on other rare types such as carcinosarcoma, squamous cell carcinoma and ONETs is insufficient, and it is difficult to achieve standardized and appropriate clinical management. Primary ONETs are uncommon malignant carcinomas with strong invasiveness and poor prognosis, accounting for less than 1–2% of ovarian malignant tumors[1]. Most patients are diagnosed with advanced stage disease[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 these tumors are usually mixed with other histological subtypes, such as mucinous adenocarcinoma, endometrioid adenocarcinoma or teratoma, which can cause mis diagnosis in the clinic[4, 5]. These tumors also express similar neuroendocrine makers such as

synaptophysin and chromogranin, thus they are grouped together[5]. Because of the low incidence of ovarian NETs, there are only limited studies to guide clinical decisions, which brings great challenges to clinical diagnosis and treatment.

This study describes 10 patients with ONETs treated at the First Affiliated Hospital of Zhengzhou University from 2015 to 2020. Their clinical data were analyzed to look for specific clinicopathological features that can be helpful to the diagnosis of ovarian NETs and to provide reference for clinical management.

Results

Ten patients with ONETs were identified and included in this study. The incidence of ONETs account for 0.49%(10/2048)of ovarian malignant tumors in our hospital. The clinical features are summarized in Table 1. The mean age at diagnosis was 38.4 years (range 20 to 58 years). All patients had no family history of ovarian cancer. One patient underwent hysterectomy for a myoma 10 years ago. The most common presenting symptoms were abdominal pain (4 of 10) or a pelvic mass (3 of 10). In two cases tumor was asymptomatic. Only one case presented with vaginal bleeding. Preoperative cancer antigen 125 (CA-125, normal range ≤ 35U/ml) levels were elevated in eight of ten patients. NSE levels were slightly elevated in two patients. These serum tumor markers returned to normal levels after treatment. All patients underwent ultrasound (US) and computed tomography (CT) before surgery. US test showed that the boundary of the mass was unclear, the shape was irregular, and there was abundant blood flow. 6 patients had ascites of varying degrees. The contrast enhanced CT showed a soft tissue mass with heterogeneous density in the pelvic cavity. No tumoral lesions were observed in the gastrointestinal tract, pancreas-hepatobiliary system or lungs on imaging scan. There was also no imaging evidence showing 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. The cut surface of the tumor was gray-white or gray-yellow. Cystic degeneration, hemorrhage or necrosis was observed. Microscopically, the tumor cells were round or oval, with abundant cytoplasm, prominent nucleoli, and active nuclear division. The immunohistochemical results are summarized in Table 2.

Table 1
Clinical characteristics of 10 patients with ONETs

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	PDS
3	31	Mass	10	IIIC	61.25	PDS
4	32	Pain	10	IIIC	146.6	PDS
5	54	Pain	5	IIIB	170.6	IDS
6	46	Mass	13	IIIC	191.0	PDS
7	29	No	8	IA	17.95	USO
8	37	No	8	IA	42.13	Staging surgery
9	51	Pain	8	IIA	120	PDS
10	58	Bleeding	4	IIIC	14.5	PDS

In terms of neuroendocrine components, the tumor cells were positive for CD56 (9/9), Syn (6/8), and Cg-A (5/7). Some cases also were positive for cytokeratin, PAX-8, and EMA. According to the staging standard of the FIGO 2014, two patient had stage IA disease, one stage IC, one stage IIA, one stage IIIB, and five patients had stage IIIC disease.

All patients underwent surgery. Two young patients had fertility requirements and were unwilling to undergo comprehensive operation. Finally, one underwent unilateral salpingo-oophorectomy (USO), the other underwent bilateral salpingo-oophorectomy

Table 2
immunohistochemical results of 10 patients 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

(BSO), omentectomy and lymph node dissection. Seven patients underwent debulking surgery (six primary surgery and one neoadjuvant chemotherapy followed by internal debulking surgery), including hysterectomy, BSO, lymph node dissection, lymph nodes dissection, omentectomy, and debulking of extra-ovarian cancer. One patient with stage IA underwent staging surgery.

Table 3
Adjuvant chemotherapy regimens and follow-up.

Case	Chemotherapy	Recurrence/Months	Follow-up(months)
1	EP	Yes/12	24
2	TC	Yes/4	10
3	EP	No	24
4	TP	Yes/6	17
5	TP	Yes/5	14
6	TP followed by Olaparib	Yes/4	20
7	EP	Yes/5	10/Died
8	EP	Yes/2	12
9	EP	No	27
10	TP and radiotherapy	No	48

Each patient was evaluated for performance status prior to chemotherapy. Ten patients were ECOG 0–1. The main chemotherapy regimens used as adjuvant therapy were listed in Table 3. Five patients treated with etoposide and cisplatin or carboplatin (EP or EC). Three of them recurred (2, 5, 12 months). Three patients received paclitaxel and cisplatin or carboplatin (TP or TC), and all of them relapsed (4, 5, 6 months). One patient was detected with BRCA2 gene mutation and was maintained with Olaparib after the end of chemotherapy, but this patient recurred after 4 months. One received chemotherapy and radiotherapy. The patient has been followed up for 48 years, and there is no imaging evidence that the tumor has recurred. The time from surgery to initiation of chemotherapy ranged 2 to 4 weeks.

The follow-up time for the ten patients ranged from 10 to 48 months. One patient died because of recurrence of disease, while the other 9 patients were still being followed up. Seven patients recurred after the end of treatment, and the time was 2, 4, 4, 5, 5, 6 and 12 months. The sites included liver, bones, pelvis, and inguinal lymph nodes. Serum CA-125 was elevated in three patients at the time of recurrence.

Discussion

The incidence of ONETs is extremely low, and the result of this study is consistent with the fact which is 0.49%. The patients were mainly in productive ages with the mean age being 38.4 years. Previous studies have reported that ovarian neuroendocrine carcinoma could also occur after menopause[6, 7]. Abdominal pain and a pelvic mass are the most common symptoms, which concurs with the findings of previous studies, suggesting these tumors lacked specific clinical manifestations. Patients have no symptoms in the early stage of the disease. Like other ovarian malignant tumors, early detection is difficult. ONETs tend to be solid and cystic, bilateral, and large. Most patients (6/10) presented with advance disease at

the time of diagnosis, which was consistent with the literature[2]. It 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 ONETs. There has been no reported on the rate of lymph node metastasis in the published literature.

US and CT usually lack specific findings in ONETs cases. A research suggested different morphological features on the magnetic resonance imaging (MRI) may indicate these rare malignant tumors[8]. However, it is far from enough to make a diagnosis by imaging test alone[9]. In this study, serum CA-125 levels were elevated in most cases (8/10) at the time of diagnosis. It seemed to indicate a link between CA-125 and these tumors. Studies have confirmed that CA-125 level is closely related to epithelial ovarian cancers and can be used for the monitoring and diagnosis of epithelial ovarian cancers[10, 11]. Therefore, further study is needed to analyzed 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, suggesting that it may be difficult to identify malignant cells derived from ONETs in ascitic fluid. Therefore, histopathological analysis of tissue specimens is crucial for the diagnosis of ONETs.

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 less one neuroendocrine marker such as Cg-A, CD56 or Syn. These markers were commonly used in most practices[12, 13]. In our study, CD56 seemed to be the most sensitive marker in demonstrating neuroendocrine nature of these tumors and was expressed in all cases. But CD56 lacked specificity because it was also expressed by nonendocrine tissues such as renal tubules, ovarian sex cord-stromal, and thyroid follicular cells[14–16]. Therefore, some authors did not recommend using CD56 alone to demonstrate neuroendocrine components[12, 14]. Syn seem to be more sensitive than Cg-A. As seen in our cases, Syn was either wore widely expressed than Cg-A or was positive when Cg-A was negative. Some cases also expressed cytokeratin, which might be useful to confirm the epithelial nature of the tumors. According to the previous study, immunohistochemical markers were useful for the differential diagnosis of ONETs. 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 usually surgical resection with adjuvant chemotherapy, but there is still no standard guideline[18]. The purpose of surgical resection is to obtain negative margins. A recent study indicated surgery significantly improved survival rates and complete surgical resection should be recommended as the primary modality[7]. In previous stage III/IV cases, most patients firstly underwent open surgery for diagnosis and treatment, and sometimes it was difficult to perform satisfactory primary debulking surgery (PDS), resulting in deterioration of patients' general condition and worse prognosis[6, 9, 12]. In our study, one case accepted diagnostic laparoscopy, finding that complete PDS cannot be performed. The patient received neoadjuvant chemotherapy followed by internal debulking surgery (NACT-IDS). The role of diagnosis laparoscopy for patients with advanced-stage ovarian cancer have been reported[19, 20], and these studies will be helpful in offering a similar method

for ONETs. Some patients diagnosed with ONETs are of childbearing age and are 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 result[21, 22]. Another study reported 26 patients underwent USO and none of the patients had a subsequent successful pregnancy[23]. In our study, two patients accepted fertility-sparing surgery. One patient who underwent BSO relapsed after 5 months of treatment and died 10 months later, and the other patient who underwent USO recurred 12 months after the end of treatment. The result was terrible. In addition, postoperative chemotherapy may also affect their ovarian function. Therefore, further research is needed to determine whether fertility-sparing surgery is reasonable for patients with ovarian neuroendocrine carcinoma.

Present adjuvant therapies are based on data arising from pulmonary or ovarian literature, including chemotherapy and radiation[2]. In this study, 60% of patients who treated with EP recurred, and 80% patients who received PT relapsed. 50% recurred within 6 months of chemotherapy, which suggested that these tumors might respond poorly to chemotherapy. Yang et al reviewed sporadic case reports, and their study did not confirm survival benefits from chemotherapy[24]. Two patients who received EP have been followed up for 24 and 27 months, without disease. The paucity of data suggests 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 patient received radiation therapy, which may be partly due to the low rate of radiation use to treat ovarian carcinoma histology. The patient has been followed up for 48 years, and there is no imaging evidence that the tumor has recurred. The role of radiotherapy in the treatment of ONETs is largely unknown, but several reports have suggested a potential benefit[25, 26]. Radiotherapy is worthy being further explored in ONETs. At present, there were few studies on targeted therapy in ONEETs. In this study, one patient with BRCA2 germline mutation was maintained with PARP inhibitors (Olaparib). The patient did not benefit from Olaparib and recurred after 4 months.

Conclusion

In summary, ONETs are uncommon malignant carcinomas and aggressive disease with poor prognosis. The diagnosis of these tumors should be based on histopathological analysis of tissue specimens, and immunohistochemistry plays an important role in diagnosis and differential diagnosis. Although large-scale case studies are lacking, we suggest that surgical resection may be the first choice of therapy, and adjuvant chemotherapy and possible radiotherapy may prolong the survival of some patients. Due to the low incidence, we recommend to establish a global database to collect and analyze these data for further study of its prognosis and therapeutic regimens.

Methods

We retrospectively analyzed ten patients 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 patients 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, including 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 used to evaluate performance status. Tumors were staged using FIGO staging classification for ovarian carcinomas.

All patient signed the informed consent for surgery before receiving treatment. This 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; CA125Cancer 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;

Declarations

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Authorsç contributions

WZ designed this study and wrote the manuscript. SC and WF participated in collection and analysis of data. LH performed the operation. MC and LL 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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