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Three case reports of ovarian neuroendocrine carcinoma

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Summary

Introduction: Being very rare entities, neuroendocrine tumors of the ovary are mostly benign while few types are malignant. Based on the WHO classification, an acceptable categorization is carcinoid, atypical carcinoid, small-, and large-cell neuroendocrine carcinomas which are of low-, intermediate-, and high-grade, respectively. In this study, the authors present three cases of ovarian neuroendocrine carcinoma. Because such large-cell tumor occurs rarely, they present the similar cases which have been reported in the past. *Cases:* The first two cases were 71- and 56-year-old women who had been referred with an ovarian mass. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) was performed and a Stage 1A ovarian carcinoid tumor was diagnosed in both cases. The two cases received no special type of adjuvant therapy following surgery and their disease-free survival rate was two and 14 years, respectively. The third patient was a 54-year-old woman who was referred with abdominal pain, symptoms of peritonitis, and a pelvic mass. A pelvic mass was found intraoperatively with extensive adhesions to the small and large intestines. She underwent right salpingo-oophorectomy and ileostomy. In pathologic study, ovarian large-cell neuroendocrine tumor and teratoma with intestinal invasion (Stage 3) were diagnosed. She received chemotherapy, then underwent TAH-LSO (TAH-left salpingo-oophorectomy) and sigmoid resection. No complication was reported in her one-year follow-up. *Conclusion:* Neuroendocrine tumors of the ovary may present with non-specific symptoms and diagnosis is made just based on pathologic evaluation.

Key words: Ovary; Teratoma; Large-cell neuroendocrine tumor.

Introduction

Being accounting for only 2% of gynecological cancers, neuroendocrine tumors of the genital tract are exceedingly rare neoplasms and can originate from the vagina, vulva, cervix, endometrium or the ovaries [1]. The most common form of neuroendocrine tumor of the ovary is the typical carcinoid tumor, while both the atypical carcinoid type and poorly differentiated neuroendocrine carcinomas are very rare. Primary ovarian carcinoids account for less than 5% of carcinoid tumors and less than 1% of ovarian tumors. They are typically unilateral with slow growth and are typically diagnosed in the early stages which are still benign. The prognosis is generally good [2] and its pathologic characteristics include limited mitosis, lack of necrosis with cytoplasm uniformity and organized architectural patterns [3].

In atypical carcinoid tumors nuclear atypia, necrosis, and immunohistochemical evidence of neuroendocrine differentiation is required for the diagnosis. They have a worse outcome in comparison to well-differentiated carcinoid tumors, but a better outcome than poorly differentiated neuroendocrine carcinomas [4]. Due to their rare occurrence, most of researchers are not familiar with the associated clinical behavior.

Ovarian neuroendocrine carcinomas which include both small- and large-cell carcinoma are highly invasive and malignant neoplasm irrespective of the disease stage [2, 4]. Ovarian large-cell neuroendocrine carcinomas have recently entered the tumors classification system, therefore, most of gynecologic oncologists are not yet familiar with this term [5]. It is diagnosed by either circular or oval-shaped large tumoral cells, a trabecular pattern, and little cytoplasm [3].

In this study, the authors present two cases of carcinoid tumors of the ovary, as well as a case of ovarian large-cell neuroendocrine carcinomas originating from an ovarian teratoma.

Case Report

Case 1

A 74-year-old woman who was multiparous and menopausal 25 years prior was admitted to Ghaem hospital, Mashhad University of Medical Sciences with chronic abdominal pain lasting

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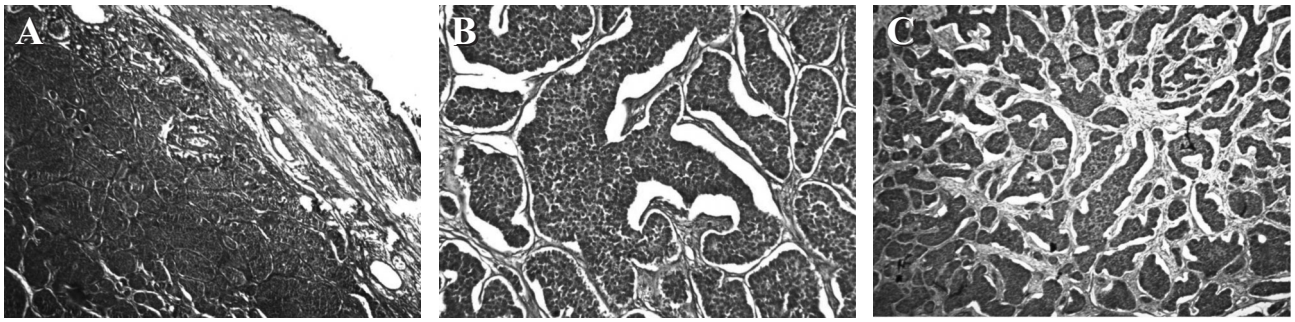

Figure 1. — A: Mucinous cyst with nests and tubules of neuroendocrine cells (×40, H&E staining). B: Trabecular cells with granular eosinophilic cytoplasm on uniform round central nuclei. C: Positive immunohistochemical staining for synaptophysin (×100).

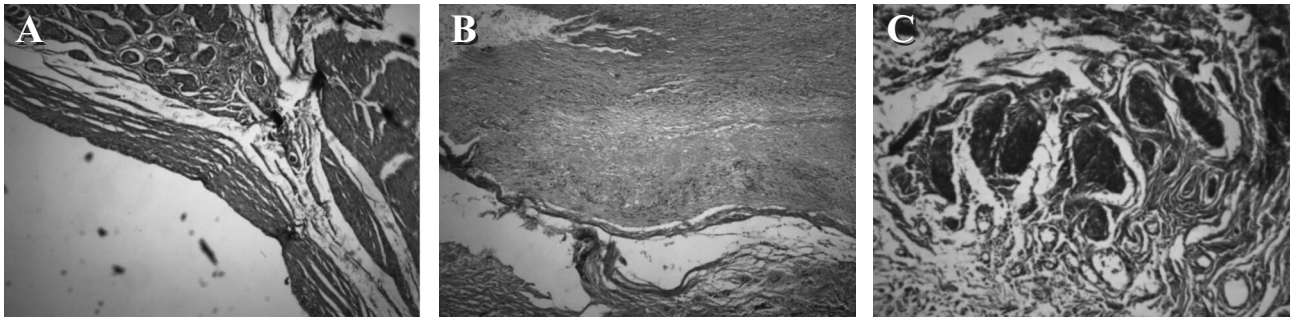

Figure 2. — A: Mucinous epithelium of muscle tissue with monomorphic and monotone cell islands and acidophilic cytoplasm creating NEST (×40, H&E staining). B: Foci of brain tissue differentiation with mucinous epithelium. C: Positive immunohistochemical staining for synaptophysin that identifies its neuroendocrine nature (×100).

five months. She had a history of chronic hypertension lasting ten years before treatment.

The general condition of the patient was stable on the physical examination. Vaginal examination revealed unilateral non-tender solid masses with mobility. Ultrasound imaging revealed a right-side adnexal complex mass with lobulated margins measuring 38×66 mm^2 containing solid nodular particles, in addition to a cystic component. Regarding lab data, CA-125 and CEA levels were reported as 45 units/ml and eight ng/ml, respectively. The patient was fully asymptomatic and there was no evidence of a carcinoid syndrome (i.e., flushing, diarrhea, abdominal cramping or cardiac involvement).

The patient underwent an exploratory laparotomy. The tumor was observed as a solid and cystic mass with size of 7×5×5 cm^3. Results of frozen section examination revealed a malignant tumor, most likely a granulosa cell tumor. Thus, the authors performed a Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO). No evidence of metastasis was found in the abdominal cavity.

Results of permanent pathologic report revealed that the peritoneal ascetic fluid was negative for malignant cells. Histological examination of the right ovarian tumor showed proliferation of the cells with granular eosinophilic cytoplasm, uniform round central nuclei with coarse chromatin and small tubule formation, and mitotic count 0-1/10 HPF. In immunohistochemical study, the result of tumoral cells were positive for CK7, chromogranin, and synaptophysin, and negative for inhibin, CK20, CEA, and TTF. The Ki-67 was 3% tumoral cells, which supported the diagnosis of carcinoid tumor (insular type). A simple mucinous cyst was also present (Figure 1). The patient had an uneventful postoperative period. The 24-hour urinary level of 5-hydroxyindoleacetic acid (5-HIAA) was also normal (three mg/24 hours). The patient remained tumor-free for two years. Abdomino-pelvic CT-scan revealed no evidence of recurrent disease. No adjuvant treatments such as radiotherapy or chemotherapy were performed.

Case 2

A 56-year-old multiparous woman with abdominal pain, nausea, vomiting, and occasional diarrhea lasting one month prior was referred to Mashhad 17 Shahrival Hospital. Due to her severe gastrointestinal (GI) symptoms, she was unable to eat on a regular basis, which resulted in a poor nutritional status and a mandatory hospitalization. On ultrasound examination of her ovaries, a bilateral multi-cystic mass with size of eight cm was diagnosed. However, the result of her tumor markers, i.e., CEA = two ng/ml and CA-125= 21 units/ml confirmed a normal condition.

No ascites were detected in laparotomy, and the uterus was of normal size. The left ovary measured 8×11×14 cm^3 and the right ovary measured 6×9×12 cm^3. Two ovarian masses had no adhesions and the other abdominal organs were normal. The patient underwent both hysterectomy and bilateral oophorectomy.

In pathologic study, a mature cystic teratoma with malignant transformation (carcinoid tumor) was diagnosed in her right ovary. In her left ovary, a mature cystic teratoma with no malignant transformation was reported. Moreover, proliferation of monomorphic and monotone cells with acidophilic granular cytoplasm, containing nuclei with a salt-and-pepper pattern as cellular nests with

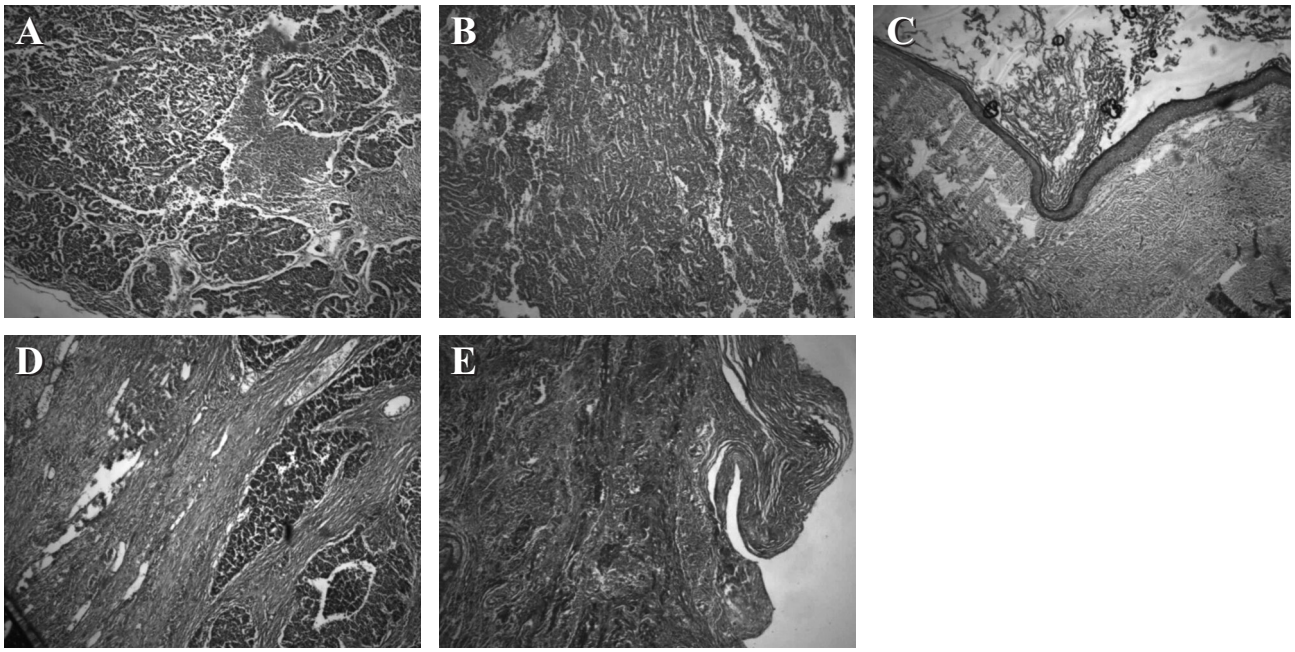

Figure 3. — A: Monomorphic and monotone cells with numerous mitotic and an extensive necrosis, insular view (×40, H&E staining). B: Ovarian tissue showing neuroendocrine carcinoma with trabecular slightly insular tissue. C: Ovarian tissue containing creatine and keratinized squamous cover. D: Invasion of tumoral tissue at the wall of ileum in which immunohistochemical staining is negative for CDx2 and CK (20) and positive for CK7 that indicates the ovarian nature of the lesion. E: Positive immunohistochemical staining for chromogranin (×100).

no atypia, mitosis or polymorphism were observed. The Ki-67 index was 2% and the morphological report was of the insular type.

The immunohistochemical report was as follows: positive for S100, positive for NSE, positive for chromogranin, and negative for cytokeratin. All of the above mentioned results confirmed a neuroendocrine carcinoma of the ovary. Moreover, the negative result of CK7 index and positive result of CK20 index in the tumor ample were indicating of an ovarian origin for the tumor (Figure 2). The patient's pain and GI symptoms were alleviated following treatment. She received no medication following surgery, and her 14-year follow-up was uneventful.

Case 3

A 54-year-old multiparous woman was referred to Ghaem hospital, Mashhad University of Medical Sciences with several complaints of severe abdominal pain, especially in the right lower quadrant during prior week before coming to the hospital. She had experienced both nausea and vomiting twice and had fever for two consecutive days. Her temperature was 40ºC, pulse rate was 100 beats per minute, and her blood pressure was 110/80 mmHg. Laboratory data were as follows: Hgb: 10.5 (g/dl), white blood cells: 8,400 (thousand/mm^3), neutrophils: 89%, lymphocytes: 9%, and platelets: 266×10^3 (thousand/mm^3)

The patient had normal bowel movements, while she felt a noticeable loss of appetite without any major loss in her weight. Abdominal tenderness and rebound tenderness were diagnosed in the hypogastric region and right lower quadrant. On speculum examination, the cervix and vagina were reported as normal with no vaginal bleeding or discharge. On bimanual examination, right adnexal fullness and tenderness were detected with cervical motion tenderness. Ultrasound study revealed a left ovarian multicystic mass with dimensions of 76×79 mm^2 and a right ovarian heterogeneous solid-cystic mass with dimensions of 125×113 mm^2 with no signs of free fluid.

Considering the primary diagnosis of adnexal torsion and the probability of a tubo-ovarian abscess, around 500 cc of malodorous pus was suctioned during abdominal laparotomy. An inflamed multi-lobulated mass of 10×15 cm^2 was diagnosed in the right adnexa with adhesions to the bladder, small intestine, and sigmoid. Her appendix was also inflamed and tumoral and was 4×3 cm^2 in size. Right SPO was performed, but because of the invasion of the tumor, the ileum had ruptured about ten cm before the ileocecal valve for which appendectomy and ileostomy was performed. An eight-cm mass was diagnosed in the sigmoid, and due to the unknown origin of the tumor, the operation was ended.

In the pathology report, the peritoneal fluid sample was negative for malignancy. The histological study of few sections of the right ovarian mass showed a mature cystic teratoma accompanying a NEC. Furthermore, other sections showed neoplastic involvement with a trabecular and reticular growth patterns, cells were arranged in a palisading pattern with large nucleated nuclei, through high mitotic activity of 20/10 HPF and were atypical. Some areas had little cytoplasm and wide foci of neoplastic necrosis. Tumor invasion to the fat tissue was observed. Through investigation of the small intestine, invasion of tumoral tissue was again prominent. Immunohistochemistry results were positive for CK7 and Ki-67 (22%), but negative for CDX2 and CK20 (Figure 3).

Following the initial operation, endoscopy was performed in which an ulcer proliferative mass was observed with size of 20 cm from the anal verge. Several biopsies were taken through luminal endoscopy which all confirmed negative test results.

Following the operation, the patient received six courses of paclitaxel/carboplatin (T&C). Seven months after the first surgery, a second operation was performed in which her uterus and left

ovary were removed. Omentectomy, ileostomy closure, rectosigmoid resection, and removal of the proximal and distal stump of the ileostomy were also performed.

In the pathology report, the left ovary which was 2×3×4 cm^3 in size, contained a benign dermoid cyst, while the other parts were tumor-free. In her one-year follow up, no recurrence occurred. She had no carcinoid syndrome symptoms, like flushing or diarrhea, and is still alive one year after the second operation.

Discussion

In this study, the authors presented their observations regarding three cases of neuroendocrine carcinomas. The first two cases were of low-grade cancer, i.e., a carcinoid tumor of the ovary, while the third case was a high-grade neuroendocrine tumor of the ovary originated from an ovarian teratoma. Until now, only six cases of this type of tumor have been reported in the literature. Among them, four cases were neuroendocrine tumors admixed with ovarian teratoma and adenocarcinoma, while only two cases were pure ovarian teratomas [6]. In general, neuroendocrine tumors are exceedingly rare neoplasms in the gynecological tract and due to their rarity, the pathologists' experience or knowledge in this field is very limited. Furthermore, specific challenges have been faced because of both tumor heterogeneity as well as lack of a standard therapeutic guidelines [1, 4].

According to the WHO pulmonary classification system, carcinoid tumor is regarded either as low-grade/grade 1, atypical carcinoid tumor as intermediate grade/grade 2, or large-cell neuroendocrine carcinoma which is referred to as high-grade/grade 3 of the gastro-entero pancreatic neuroendocrine tumors classification [1].

Neuroendocrine tumors are a group of malignancies that originate from the diffused system of neuroendocrine cells (the neural crest) and have enzymatic properties. From a pathologic perspective, the main similarity of these tumors lies in the presence of similar neuroendocrine tumor markers (synaptophysin and chromogranin and neuron-specific enolase). Carcinoid tumors differ from ovarian large-cell neuroendocrine carcinomas regarding the pathology, clinical outcome, mitotic activity, atypia, and cellular necrosis points of view [4].

In the first two cases of the present study, carcinoid tumors which were observed with a mitotic count of 0-1/10 HPF, have been recorded with little atypia, no necrosis or monomorphic cells, and a low Ki-67 level. On the other hand, the third case was a large-cell tumor with high mitotic activity of 20/10 HPF and remarkable atypia, large nucleated nuclei, and extensive necrosis. Ki-67 was positive in 22%.

Carcinoid tumor which is often asymptomatic and diagnosed accidentally in ultrasound study, can be classified into five subgroups of insular, trabecular, mucinous, stromal, and mixed (insular and trabecular). The insular type, the most common form of this tumor, is usually unilateral and diagnosed in the low-stages of the disease. If such tumors are limited to the ovaries, their ten-year survival will be 100% [4]. Around 30% of patients in this subgroup have experienced symptoms of carcinoid syndrome, including flushing, diarrhea, abdominal pain, bronchospasm, and edema [2, 4], while in the other subgroups, the carcinoid symptoms of the syndrome are less common, i.e., only 13% of the trabecular and 3.2% of the stromal types [2]. Both of the present carcinoid cases were detected both as the insular type and in the first stage of the disease. The first case did not have any problem in the two-year follow-up, while the second case was disease-free over a 14-year follow-up period. Furthermore, the first case had no symptoms of carcinoid tumor whereas the second case had GI symptoms which clearly improved following surgery.

The trabecular type of carcinoid tumor is the second most common form of this tumor. In 25% of cases, it is accompanied with constipation due to the secretion of the *yy* peptide which results in reduced bowel movement [2, 4]. The carcinoid mucinous form which is rare (1.5%) has a more aggressive behavior and is accompanied with invasions to extra-ovarian sites and lymph node involvement. Primary large-cell neuroendocrine carcinoma of the ovary is a rare tumor and is now included in the WHO tumor classification. According to the WHO, this tumor is synonymous with "undifferentiated carcinoma of non-small cell neuroendocrine type" [3].

In immunohistochemical studies, the first case was positive for synaptophysin and chromogranin and CK7. However, the result of CK20 and inhibin was negative. This indicates a neuroendocrine tumor with an ovarian origin. In the second and third case, immunohistochemical studies revealed a positive test result for synaptophysin, nes, and chromogranin, while S100 result was negative which clarifies the neuroendocrine nature of the tumor. Besides, CK7 result was positive, and both CK20 and CDX20 index were negative. This shows that the primary origin of the tumor was the ovaries and was not metastatic from the intestines. Ovarian carcinoid tumors are mostly admixed with ovarian teratomas and are rarely associated with surface epithelial tumors. However, large-cell neuroendocrine carcinomas are rarely seen in association with ovarian teratomas [6, 7].

The present first case was carcinoid tumor of the ovaries admixed with a simple mucinous cyst which is also very rare. The second case was an ovarian carcinoid tumor with bilateral ovarian teratoma which is the most common co-existing form of carcinoid tumor with ovarian tumors. According to performed searches, the present third case was the third reported case of admixed pure teratoma and large-cell neuroendocrine carcinoma in the literature, which is the rarest type.

Searches in both PubMed and Google platforms revealed that there are 53 cases of large-cell neuroendocrine carcinomas in total, including the present case. The results are summarized in Table 1. The hypothesis is based on the fact that large-cell neuroendocrine carcinomas are often a result of

Table 1. — *Clinicopathologic features of 53 cases of neuroendocrine carcinomas of the ovary.*

Authors	Component	Age years	Chief complain ton	Size &side tumor	CA125 U/ML	stage	operation	Adjuvant therapy	Follow up
1. Miyamoto et al (66)	Mature cystic teratoma	69	Abd pain	15cm/L/s	37.5	IV	LSO+ debulking surgery	T&C (2 cycles)	DOD=6M
2. Versaet al(7)	Mature cystic teratoma	25	Abd pain	5cm/R	unclear	IV	BSO+OM+APP	CIS-based Che (at least 6 cycles)	DOD=36M
3. This study	Mature cystic teratoma	54	Abd Pain, Fever, vomiting	15cm/R/S	unclear	III	First=RSO+APP+ileostomy Second=TAH+LSO+OM+ Resection of rectosigmid	T&C(6 cycles)	NED=12M
4. Chenevert et al (8)	Mucinous Ac and teratoma	53	Abd dis	20cm/L/S &C	80KU/L	IV	TAH+BSO+OM+ Left iliac LYM	T&C(3 cycles)	DOD=5M
5. Chenevert et al (8)	Mucinous Ac and teratoma	53	Abd girth	21cm/L/S &C	109ku/L	IV	TAH+BSO+OM+ Left pelvic LYM (sampling)	CIS & etoposide	DOD=7 M
6. Veras et al(8)	Ac,NOS,mature teratoma	47	Abd bloating	14cm/R	Un clear	III	TAH+BSO	CIS-based Che (at least 6 cycles)	NED=11M
7. Hirasawa (9)	Mucinous Ac and teratoma	56	Abd pain	18cm/R	190	IIC	TAH+BSO+LYM	refused	DOD=10M
8. Eichhorn et al (10)	Endometroid Ac	7777	Pelvic mass/pMB	15 cm/ S &C	unclear	IA	TAH + BSO +Lymph nodes & Peritoneal BX	radiation (Refused che)	DOD=19M
9. Ohira et al (11)	Endometroid Ac	33	Abd Pain fatigue	11cm/L/ S &C	4681	IC	LSO+OM	Irinotecan and nedaplatin/4 cycles	DOD=6M
10. Oshita et al(55)	Endometroid Ac	42	Abd mass	13cm/L/S&C/R ovary metastasis	775.2	IIIB	TAH+ BSO+ optimal debulking	T&C (6 cycles)	NED=32M
11. Oshita et al(55)	Endometroid Ac	80	Abd mass	7cm/L/ S &C	204.3	IIC	TAH+BSO+OM+PEIVIC LYM+APP	T&C (6 cycles)	NED=40 M
12. Veras et al(7)	Endometroid Ac	63	ASCITES	14cm/L	Un clear	IV	TAH+RSO	CIS-based Che (at least 6 cycles)	DOD=9M
13. Veras et al(7)	Endometroid Ac	53	ASCITES	14.5cm/L	unclear	III	TAH+BSO	CIS-based Che (at least 6 cycles)	NED=37M
14. Oshita et al(55)	Endometroid AD + Squamous differentiation + mucinous Ac	65	Abd dis + nausea	15cm/L Cystic with Enhanced nodule	77	lc	TAH+BSO+OM	T&C	DOD=2M
15. Veras et al(7)	Endometroid and Mucinous Ac	54	Pelvic mass	14 cm/R/S&C	unclear	I	TAH+BSO	CIS-based Che (at least 6 cycles)	NED=66M
16. Veras et al(7)	Bening cyst and dermoid in contralateral ovary	42	Pelvic pain	Size Unknown & Cystic	Unclear	IV	TAH+BSO	CIS-based Che (at least 6 cycles)	DOD=20M
17. Asada et al(12)	mucinous adenoma	50	Abd dis	15*12*10 cm	NL	IA	TAH+BSO+OM+ PELVIC LYM	Etoposide&cis (3cycles) Second line=T&C	DOD=10M
18. Ahmed et al(13)	Benign mucinous cyst adenoma	30	Unclear	15*12*1111*12* 15cm/S&C	Unclear	Unclear	TAH+BSO	Unclear	Unclear
19. Jones et al(14)	Mucinous cyst adenoma	65	Abd dis	16*13*9cm	215	IA	TAH+BSO+OM+APP+ LYM (sampling)	Not treatment	DOD=10M
20. Hirasawa (9)	Mucinous adenoma	35	unclear	unclear	unclear	IC	TAH+BSO+OM	CDDP?	NED=10 YEARS
21. Veras et al(7)	Mucinous BLT	55	Vaginal bleeding	13.5cm/R/ S&C	unclear	III	TAH+BSO	CIS-based Che (at least 6 cycles)	DOD=2M
22. Ding et al (15)	Mucinous BLT	70	Abd dis &Weight gain	1616cm/L	10	IA	TAH+BSO+OM+APP+ pelvic LYM	Not treatment	NED=6M
23. Yasuoka et al (16)	Mucinous BLT	36	weight loss, abd dis	26CM/R/S&C	unlear	IIIC	TAH+BSO+OM+LYM	che	NED=6M
24. Sun et al (17)	Mucinous BLT And sarcomata's area	21	Abd Discomfort & pelvic mass	5cm/R	BHCG= 258 PTH=88.6	IA?	RSO	First line=bep (3 course) Second line=T&C(weekly)	DOD=5M
25. Veras et al (7)	Mucinous BLT And intraepithelial CA	55	Abd pain	26cm/R/ Cystic with Mural nodule	unclear	I	TAH+BSO	CIS-based Che (at least 6 cycles)	NED=68M
26. Veras (7)	Mucinous BLT And mucinous Ac	22	Abd pain	21cm/R/ S&C	unclear	I	RSO+APP	CIS-based Che (1cycle)	DOD=3M
27. Eichhorn et al (10)	Mucinous BLT And foci of mucinous AC	58	Pelvic mass	30cm/left/S&C	unclear	IIIB	TAH+BSO+OM+APP+ Peritoneal BX+LYM	che	DOD=8M
28. Eichhorn et al(10)	Mucinous BLT And foci of mucinous AC	45	Abd dis+pain	18cm/R/S&C and microscopic involvement of left ovary	unclear	IB	TAH+BSO+OM	che	DOD=3 YEARS
29. Khurana Et al(18)	Mucinous BLT And focal of mucinous AC	22	Abd dis+ Pain	21*15*12cm/R/S &C	unclear	IA	RSO+APP	C &CYC	DOD=3M
30. Collins et al(19)	Mucinous BLT And focal of mucinous AC.	34	Abd dis+weight loss	16*11*8cm/left..s.c	591.8	IC	TAH+BSO+OM	CIS+CYC (7course)	DOD=8M
31. Lee jj et al (20)	Mucinous tumor (benign, borderline, and malignant)	40	Abd dis	30cm/L/ S&C	88	IA	TAH+BSO+OM+APP+LYM (pelvic& para aourote)	T&C	NED=8M

Authors	Component	Age years	Chief complain ton	Size &side tumor	CA125 U/ML	stage	operation	Adjuvant therapy	Follow up
32.KIM JM et al (21)	Mucinous BLT &micro invasive mucinous Ac	35	Abd dis	15*10*7/R/S&C	473.93		TAH+BSO+ partial OM, APP+ multiple peritoneal BX	T&C	DOD=4M
33. Ei chhorn(10)	Mucinous AC	68	asymptomatic	9cm/R/s.c	Un clear	IIA	TAH+RSO +OM+ peritoneal Bx (prior LSO)	unknown	Lost to follow up
34. Veras et al (7)	Mucinous AC	39	Abd pain	Bilateral 26cm/L & R ovary (metastasis)	Un clear	IV	TAH+BSO	CIS-based Che (at least 6 cycles)	Alive with disease=8m
35. Chen (22)	Micro invasive mucinous ac	73	Abd mass	11*10*7cm/L/S&C	unclear	IIIC	BSO+OM+ prior TAH+ LYM(BX)	T&cis (7 cycles) Second:adriamcin	DOD=8M
36. Chen (22)	Mucinous AC.	44	Dyspnea, adb dis, pain	24cm/L/S&C	unclear	IA	TAH+BSO+OM	T&C	DOD=4M
37. Eichhorn et al(10)	Mucinous AC.	36	RLQ Pain +fever gurding	10cm/R/S&C	unclear	IA	RSO+APP (prior TAH)	Un clear	unclear
38. Veras (7)	High grade AC	59	Abd pain	14cm/left cystic	unclear	I	BSO	CIS-based Che (at least 6 cycles)	NED=28M
39. Draganova et al(23)	Serous carcinoma With mucin production	68	Abd distension	7 cm.R 5cm.L	1235u/ml	IIIC	Interval debulking / BSO +OM + tumor debulking	First:T&C.6 cycles. Second line:doxil.2 cycels	DOD=7M
40. Choi et al(24)	Serous carcinoma	71	Abd dis+ abd pain	6.5cm.R.S.C	Un clear	IIIB	TAH+BSO	T&c/8 CYCLES	NED=8M
41. Taube et al(25)	High grade serous Carcinoma.	55	In crease Tumor marker	Peritoneal Carcinomatosis (prior Surgical debulking)	unclraer	Pt3c,G3 ???	Secondary cytoreductive surgery	T&C (6cycles)	DOD=13M??
42.Hide et al(26)	Serous carcinoma	54	Abd dis	Pelvic mass=15 cm Bilateral/S &C	negative	IIIC	BSO+OM+sub optimal surgery	T&C (8 cycles)	NED=8M
43. Tsuji et al(27)	Pure/ focal Squamous differentiation	46	Abd Dis+ fatigue	15cm/R/S	914u/ml	IIIC	Sub total TAH+BSO+OM	T&C (2 cycles)	DOD=4M
44. Shakuntala et al (28)	Pure	40	Abd dis Fever, Itching	7cm/R 15cm/L s.c	280.80u/ml	IIIC	BSO+optimal debulking (prior TAH)	Etoposide&cis (5 cycles)	NED=9M
45.Oshita et al(5)	pure	66	Pelvic mass	11 cm/R/S&C	6595u/ml	IV	TAH+BSO+OM+ peritoneal Bx	T&C (4 cycles, NAC) Whole brain radiation	NED=64M
46. Behnam et al (29)	pure	27	Pelvic Mass	17*15.8*7.5Cm/ L/S&C	Unclear	IA	LOS+OM+APP+LYM (para aortic)+ R ovary (Bx)	T&C (6 CYCLES)	NED=10M
47. Dundr et al(30)	pure	73	dysartria	9*7*7cm/L/S	94u/ml	IV	TAH+BS+OM+ L Nephrectomy+ debulking surgery	T&C & Gamma knife (CNS recurrence)	NED=12 M
48. Lindboe (31)	pure	64	Abd Discomfort & nausea	14CM/R/S	380u/ml	IA	TAH+BSO+OM	BEP	NED=9M
49. Aslam et al(32)	pure	76	Abd pain	30cm/L/S&C	NL	IIB	TAH+BSO+OM+LYM	died before che	septic shock after operation
50. C-H Lin et al (33)	pure	50	Pelvic mass	25cm/L	685.8 u/ml	IV	TAH+BSO+ partial OM+APP	T&C (3 cycles)	DOD=3M
51. Ki et al (34)	unclear	77	Abd dis	15cm/	124 u/ml	IV	TAH + resection of pelvic and neck masses	Etoposide & carboplatin (1 cycles)	DOD=45 days (septic shock)
52. Ki et al (34)	unclear	58	Abd discomfort	L	1.6 u/ml (recurrence)	IA	TAH+BSO+OM+ LYM (BX) /second: debulking surgery	T&CIS(6 cycles) Second line=Docetaxel	DOD=17M
53. Ki Et al(34)	unclear	67	Urinary frequency	13cm/L/S&C	71.8 u/ml	IIB	TAH+BSO+OM+LYM	T&C	NED=5M

abd=abdominal, L=left, s=solid, LSO=left Salpingo-oophorectomy, T=paclitaxel, C=carboplation, DOD=dead of diseases, M=months, R=right, BSO=bilateral Salpigo-oophorectomy, OM=omentectomy, APP=appendectomy, CIS=Cisplatinum, che=chemotherapy, RSO=right Salpingo-oophorectomy, NED=no evidence of disease, AC=adenocarcinoma, dis=distension, S&C=Solid and cystic, LYM=lymphadenectomy, BLT=borderline tumor, NOS=Not otherwise specified, PMB=post-menopausal bleeding, BX=biopsies', bep=bleomycin and etoposide and cisplatinum, CYC=Cyclophosphamide.

either neuroendocrine cells' manifestation on epithelial stromal tumors or teratomas [3]. Including the present case, there are only seven cases of large-cell neuroendocrine carcinomas with ovarian teratoma reported in the literature [6, 8, 9]. In four cases, it was admixed with adenocarcinoma and mature teratoma. In the two other cases, including the present case, pure teratoma was admixed with large-cell neuroendocrine carcinoma. The patients' age ranged from 25 to 69 years. The average age of the seven aforementioned patients was 51 years, while the average tumor size ranged from 5 to 21 cm. The average tumor size was 15 cm. It was right-sided in four cases and left-sided in the rest. In six cases, the tumors were in Stage 3 and 4, and in Stage 2 in only one case.

Three patients were referred with abdominal distension, while other three cases had complaints of abdominal pain. The current case presented with abdominal pain, fever, and symptoms of acute abdomen. The CA125 data of four patients were available, and their mean level was 104 u/ml. All patients, except one case who refused chemotherapy, had undergone postoperative chemotherapy. Five cases (71%)

passed away during the first postoperative year (range: five to 36 months). Two other cases were disease-free after 11 and 12 month follow-ups. In general, large-cell neuroendocrine carcinomas originating from a teratoma have a very poor prognosis and are mostly in the higher stages of the disease when is diagnosed [6, 8].

Despite being in stage three, the present case was urgently operated with a diagnosis of acute abdomen and the suspicion of tubo-ovarian abscess, with invasions to the intestinal lumen, underwent ileostomy, and finally recto-sigmoid resection, which responded well to treatment and remains disease-free during the first-year follow up.

In the literature, eight cases of large-cell neuroendocrine carcinomas accompanied with endometrial carcinoma were found and in two cases, endometrial carcinoma was admixed with mucinous carcinoma [5, 7, 10, 11]. The patients' age ranged from 33 to 80 years, with an average age of 58 years. Four cases were in Stage 1 and others were in Stage 3 or 4 of the disease. The mean tumor size was 13 cm. Four patients passed away with a duration period of two to 19 months, with an average time of 6.5 months. Generally, four patients were disease-free in the mean follow up period of 44 months and appeared to be more benign in comparison to teratoma originated large-cell neuroendocrine carcinoma. large-cell neuroendocrine carcinoma has been reported admixed with a mucinous tumor in 21 cases; it was benign mucinous in four cases [9, 12-14] and in the other 14 cases. It coexisted with borderline mucinous and mucinous adenocarcinoma [7, 10, 15-19]. Their mean age was 46 years, with and average age ranging from 22 to 73 years. The average tumor size was 19 cm ranging from five to 30 cm. Fourteen cases were in either Stage 1 or 2, while the other five cases were in either Stage 3 or 4. The disease stages were not recognized in the other cases. Regarding patients follow-up, results of three cases were not clear enough. Ten cases passed away with a mean duration of nine months, with a range from two to 36 months.

Four cases large-cell neuroendocrine carcinomas were reported admixed with serous adenocarcinoma [23-26]. Their average age was 62 years, with a range from 54 to 71 years. All patients were in Stage 3 or 4 with average tumor size of nine cm. Two cases died with a mean follow-up period of ten months, while the other two cases survived with a mean follow-up period of eight months.

In 8 cases, the ICNCE index had no association with surface epithelium. Considering Tsuji *et al.* case [5, 27-33], the average age of patients was 55 years, with a range from 40 to 76 years. The mean tumor size was 17 cm. Three cases were in Stage 1 or 2, while the other five were either in Stage 3 or 4. Three cases passed away with a mean follow-up of two months, while five of them survived with a mean follow-up period of 20 months. In three cases reported by Ki *et al.* [34], the ovarian epithelium was not specified with large-cell neuroendocrine carcinoma. In general, the most common tumor admixed large-cell neuroendocrine carcinoma is mucinous tumor, and the least common one is a pure teratoma. The age of 53 patients ranged from 22 to 80 years, with an average of 53 years. In 25 cases, patients were either in Stage 1 or 2, while the other 24 patients were either in Stage 3 or 4. The disease stage was unknown in one case. In 27 cases, the patients passed away in less than ten months, and 19 patients survived over a mean follow-up of 29 months. The follow-up outcome of four patients were unknown. Due to the rarity of large-cell neuroendocrine carcinoma cases, limited data about the treatment of such patients are available. They often undergo primary surgery and tumor debulking operation which are followed by chemotherapy. No ideal chemotherapeutic regimen has been introduced for such patients. However in most cases, such patients received T&C chemotherapy [3]. Based on the available data, 21 patients among the entire 53 patients received T&C treatment. Other 17 patients received cisplatinum with etoposide, cyclophosphamide or paclitaxel. One patient did not consent to receive chemotherapy and therefore underwent radiotherapy instead. Neoadjuvant therapy was administered in two patients. The present patient received six cycles of T&C following her surgery.

In contrast to large-cell neuroendocrine carcinomas, patients with carcinoid tumors have a better prognosis, especially in the initial stages. In case of young patients with unilateral tumors, fertility-sparing surgery may be performed, and radical debulking depends on the patient's age and the disease distribution. Thus, there is no need for using adjuvant therapy of any type such as chemotherapy, radiotherapy or hormone therapy in gynecologic carcinoid tumors [4].

In the present first case with a carcinoid tumor, TAH+BSO +STAGING treatment was performed, mainly because of the patient's age, as well as the result of frozen section of patient which showed suspicious of granulosa cell tumor, and was recognized in Stage 1A. Having received none of the types of following surgery treatment, the patient was event-free during the two-year follow up. In the second case, a TAH+BSO treatment was performed without staging, mainly because of patients' age and a bilateral ovarian tumor. In this case, there was no other therapeutic modality following surgery, and occurrence was not observed in 14-year follow-up.

Conclusion

Neuroendocrine tumors of the ovary may be presented by non-specific symptom. There are different treatments depending on the type and the final diagnosis is performed by the pathologist, and are divided into three categories based on the degree of cellular atypia, mitosis, and necrosis. In this study, the authors presented three cases of ovarian neuroendocrine tumor. The first two cases with low grade ovarian neuroendocrine tumors had a good prognosis and the need for extensive surgery or adjuvant therapy

was not essential. The third case was a large-cell neuroendocrine carcinoma originating from an ovarian teratoma with high atypia and mitosis and extensive necrosis in pathology report. Being absolutely rare and malignant, the referred patients (with acute abdomen) required extensive surgery and chemotherapy after surgery.

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