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Ovarian yolk sac tumor in postmenopausal females

A case series and a literature review

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Abstract

Rationale: Ovarian yolk sac tumors (YSTs) are the second most common histologic type of ovarian germ cell tumors. Most patients are adolescent and young women, while cases in postmenopausal women were rarely reported. Due to its rarity, we know little about the treatment and prognosis of postmenopausal patients with ovarian YSTs. We reported 3 cases of mixed ovarian YST in postmenopausal females reviewed the related current English literature.

Patient concerns: The ages of the three patients were 61, 58 and 77 respectively. The three patients came to the hospital because of the abdominal discomfort or tenderness, and the third patient also has vaginal bleeding.

Diagnoses: Imaging examination revealed pelvic mass with cystic and solid components. The elevated serum AFP level and pathologcial examination confirmed mixed ovarian YST.

Interventions: All patients received surgery and chemotherapy. Two patients received PEB (cisplatin, etoposide, and bleomycin) chemotherapy initially and one patient received TC (paclitaxel carboplatin) chemotherapy.

Outcomes: One patient relapsed 8 months after diagnosis and underwent re-cytoreductive surgery. The three patients all survived at last follow-up.

Lessons: The diagnosis of postmenopausal ovarian YST is relatively difficult and it can coexist with other germ cell or epithelial tumors. Postmenopausal ovarian YSTs are aggressive, and may have a worse prognosis compared with those in young patients. More aggressive treatment is needed. When YST mixed with epithelial cancer components, adjuvant chemotherapy regimen should include platinum-based chemotherapy aiming at both epithelial ovarian cancer and germ cell tumors.

Abbreviations: AFP = a-fetoprotein, BSO = bilateral salpingo-oophorectomy, CA125 = cancer antigen 125, CEA = carcinoembryonic antigen, OGCT = ovarian germ-cell tumor, PEB = cisplatin, etoposide and bleomycin, PEV = cisplatin, etoposide and vincristine, TAH = total abdominal hysterectomy, TC = paclitaxel-carboplatin, YST = yolk sac tumor.

Keywords: ovarian germ cell, postmenopausal, prognosis, yolk sac tumor

1. Introduction

Ovarian germ-cell tumors (OGCTs) comprise about 15% to 20% of all ovarian tumors and 2% to 5% of all ovarian malignancies.[1] Ovarian yolk sac tumors (YSTs) account for 14% to 20% of all malignant OGCTs. The age distribution of patients reported with YST ranges from 16 months to 86 years, but two-thirds of them are under 20 years of age, occasionally in postmenopausal women.[2] Postmenopausal patients may have different characteristics and prognosis from those of child-bearing age patients. The majority of YSTs in postmenopausal patients are associated with epithelial ovarian carcinoma and appear to be associated with a poorer outcome.[3] There is little knowledge concerning the development, treatment, and outcome of postmenopausal YSTs. To provide additional knowledge to this rare disease, we present 3 cases of ovarian YST in postmenopausal females diagnosed and treated in our hospital from 2000 to 2017. Based on a review of these cases and the related current literature on this topic, we attempted to enhance the understanding of this rare entity.

2. Methods

This study retrospectively analyzed the data of postmenopausal patients with ovarian YST who were diagnosed and treated from 2000 and 2017 in Peking Union Medical College Hospital. The study protocol was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the

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Table 1

Clinicopathologic details of cases in present study.

Case	Age	CA125, U/mL	AFP, ng/mL	Surgery	Stage	Pathology	IHC	Chemotherapy	Outcome
1	61	59.8	Preoperative: 1847	TAH+BSO+PLN+PALN +Appendectomy +Omentectomy +Metastatic tumor resection	IIIB	YST+LGSPC+IT	F: AFP, SALL4, EMA, CD99, PR N: OCT3/4, CD30, P53, S-100, NF	PEB × 2 PEV × 1 TC × 1	Recurrence: 8 mo Alive at 23 mo
2	58	Normal	Preoperative: 219.7	TAH+BSO+PLN+PALN+ Appendectomy +Omentectomy	IC	YST+CCC	F: AFP, SALL4, PAX-8, EMA, CK7, CD20 N: p53, WT-1, PR-, ER-, OCT3/4	PEB × 3	DF: 12 mo
3	77	555.8	Preoperative: NA After 1st TC chemotherapy: 27,356	Interval cytoreductive surgery (BSO+Omentectomy metastatic tumor resection)	IIIC	YST+HGSC	D: AE1/AE3, CK7, p53 F: AFP, SALL4	NACT: TC × 3 After surgery: TC × 1	DF: 7 mo

AFP = a-Fetoprotein, BSO = bilateral salpingo-oophorectomy, CCC = clear cell carcinoma, D = diffuse (≥50%), EMA = epithelial membrane antigen, ER = estrogen receptor, F = focal (<50%), HGSC = high-grade serous carcinoma, IT = immature teratoma, LGSPC = low-grade serous papillary cystadenocarcinoma, N = negative, NACT = new adjuvant chemotherapy treatment, P = positive, PALN = para-aortic lymphadenectomy, PEB = cisplatin, etoposide and bleomycin, PEV = cisplatin, etoposide and vincristine, PLN = pelvic lymphadenectomy, PR = progestogen receptor, TAH = total abdominal hysterectomy, TC = paclitaxel and carboplatin.

Institutional Ethical Committee of Peking Union Medical College Hospital. All patients signed an informed consent.

The information of postmenopausal patients with ovarian YST, including patient's age at diagnosis, chief complaint, clinical features, tumor markers, imaging findings, surgical records, pathology, treatment modality, and follow-up were recorded. All surgical specimens were re-evaluated by 2 specialized gynecologic pathologists.

3. Results

A review of our database revealed 3 postmenopausal patients diagnosed with ovarian YST (Table 1) and their pathology were confirmed by 2 gynecologic pathologists.

3.1. Case 1

A 61-year-old woman presented with a 2-week history of lower abdominal discomfort when urinating, and an abdominal mass was palpable on examination. No family history of cancer. The computed tomographic (CT) imaging demonstrated a pelvic mass disease with mixed density (Fig. 1). Preoperatively, cancer antigen 125 (Ca125) was 59.8 U/mL (normal, 0–35 U/mL), and a-fetoprotein (AFP) was 1847 ng/mL (normal, 0–20 ng/mL) (Fig. 2). The patient underwent primary cytoreductive surgery with total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), pelvic and para-aortic lymphadenectomy, appendectomy, and omentectomy and metastatic tumor resection without macroscopic residual disease. Surgery reviewed a mass arising from the right ovary with involvement of the surface of left ovary, transverse colon surface, the omentum, the right paracolic sulcus, mesentery of the small intestine, uterosacral ligament, right pelvic peritoneum, anterior rectal wall, ileocecal mesangial, and mesoappendix. The FIGO stage was IIIB.

3.1.1. Histopathologic findings. The postoperative pathology reported this tumor to be a low-grade serous papillary cystadenocarcinoma and mixed germ-cell tumor (immature teratoma and YST) affecting the right ovary. The tumor showed patchy strong positivity for SALL4 and AFP. They also showed focal positivity for epithelial membrane antigen (EMA), cluster of differentiation 99 (CD99), and progestrone receptor (PR). The tumor was negative for octamer 3/4 (OCT3/4), CD30, P53, S-100, and NF.

3.1.2. Treatment and outcome. Postoperative AFP was decreased to be 203.0 ng/mL and CA125 was 71.1 U/mL (Fig. 2). The patient received 2 cycles of PEB (cisplatin, etoposide and bleomycin) chemotherapy. Due to the decline of pulmonary diffuse function, the 3rd cycle regimen was changed to PEV (cisplatin, etoposide, and vincristine). Because of the intolerance of the side effects, the patient received a 4th course of TC (paclitaxel and carboplatin) chemotherapy and stopped treatment. After 8 months of diagnosis, the patient developed intestinal obstruction, suggesting a recurrence of the tumor with normal serum AFP level. The patient received a second cytoreductive surgery (massive resection of small intestine). Because of poor physical condition, she did not receive any chemotherapy. She currently survived for 23 months.

3.2. Case 2

A 58-year-old postmenopausal woman was admitted for lower abdominal tenderness and a pelvic mass. CT scan demonstrated a complex right adnexal mass with cystic and solid components (Fig. 3). The preoperative AFP was 219.7 ng/mL, while carcinoembryonic antigen (CEA), CA125, and CA199 were within the normal range. TAH, BSO, pelvic and para-aortic lymphadenectomy omentectomy and appendectomy were performed.

3.2.1. Histopathologic findings. Pathology revealed a clear cell carcinoma arising from the right ovary with YST component (Fig. 4). There are multiple leiomyoma and adenomyosis in uterus. The malignant tumor was confined to the right ovary; no metastases were found. Her FIGO stage was IC. Immunohistochemical staining showed germ cells were positive for SALL4 and AFP, and were negative for p53, OCT3/4, Napsin A, progestrone receptor (PR), and estrogen receptor (ER). In clear cell carcinoma component, CK7 and EMA were diffusely positive and SALL-4 was focally positive.

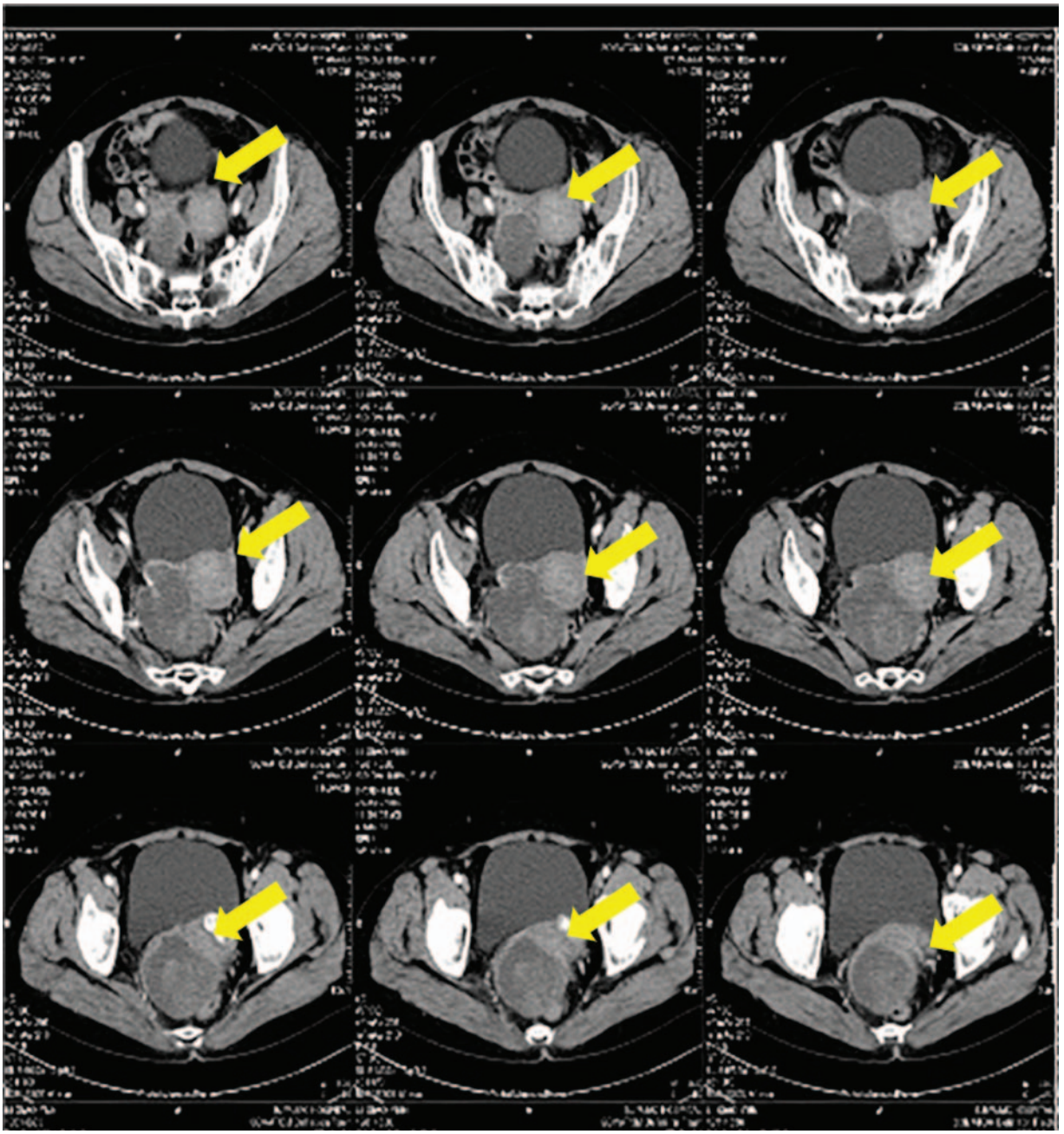

Figure 1. Case 1: Preoperative computed tomography images.

3.2.2. Treatment and outcome. After surgery, she received 3 courses of chemotherapy with PEB regimen. Changes in serum AFP levels during chemotherapy are shown in Figure 5. Due to the severe bone marrow suppression, the patient terminated chemotherapy after 3 cycles of PEB chemotherapy. At the current follow-up, there were no signs of tumor recurrence.

3.3. Case 3

A 77-year-old multiparous woman with a 1-month history of lower abdominal discomfort and vaginal bleeding. CT imaging showed multiple solid and cystic pelvic mass (Fig. 6). Positron emission tomography-computed tomography(PET-CT) revealed complex solid and cystic pelvic mass located in the bilateral adnexa and posterior of uterus. There were multiple metastases on mesentery and peritoneum. A preoperative serum CA-125 was 555.8 U/mL and CA199 was 58.2 U/mL. Serum AFP was not performed preoperatively. The gastrointestinal endoscopy examination was negative. The patient subsequently underwent a laparoscopic exploration, patches of biopsies, and curettage. Intraoperatively, multiple metastatic nodules scattered in the omentum and the diaphragm (Fig. 7A). The bilateral annexa was wrapped by omentum, revealing a small part of the mass (Fig. 7B). Postoperative pathology revealed undifferentiated carcinoma of pelvic mass and high-grade serous carcinoma of endometrium. After 3 cycles of TC, she underwent interval cytoreductive surgery. The second postoperative recovery was good, and she received the third TC chemotherapy. Changes in

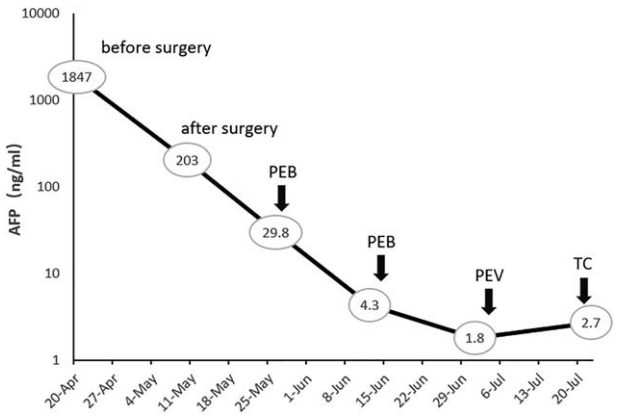

Figure 2. Case1: Changes in serum a-fetoprotein (AFP) levels during chemotherapy. PEB = cisplatin, etoposide and bleomycin, PEV = cisplatin, etoposide and vincristine, TC = paclitaxel and carboplatin.

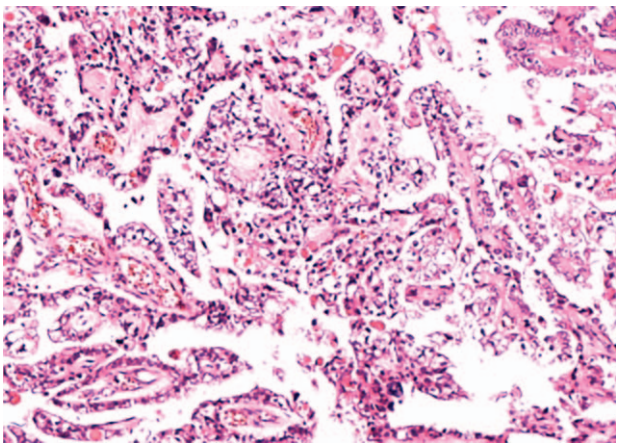

Figure 4. Case 2: Clear cell carcinoma component with yolk sac tumor (hematoxylin and eosin, ×100).

serum AFP levels during chemotherapy and surgery are shown in Figure 8.

3.3.1. Histopathologic findings. Pathology revealed bilateral ovarian high-grade serous carcinomas with YST differentiation involving the surface of omentum, bladder, and rectum. The tumor displayed focal-positive staining for AFP and SALL4. AE1/AE3, CK7, and p53 were diffusely positive. There was negative staining for PAX-8, ER, PR, OCT3/4, and WT-1.

3.3.2. Treatment and outcome. The patient refused to continue chemotherapy after receiving 1 course of TC chemotherapy postoperatively. There are no signs of tumor recurrence at a follow-up of 7 months.

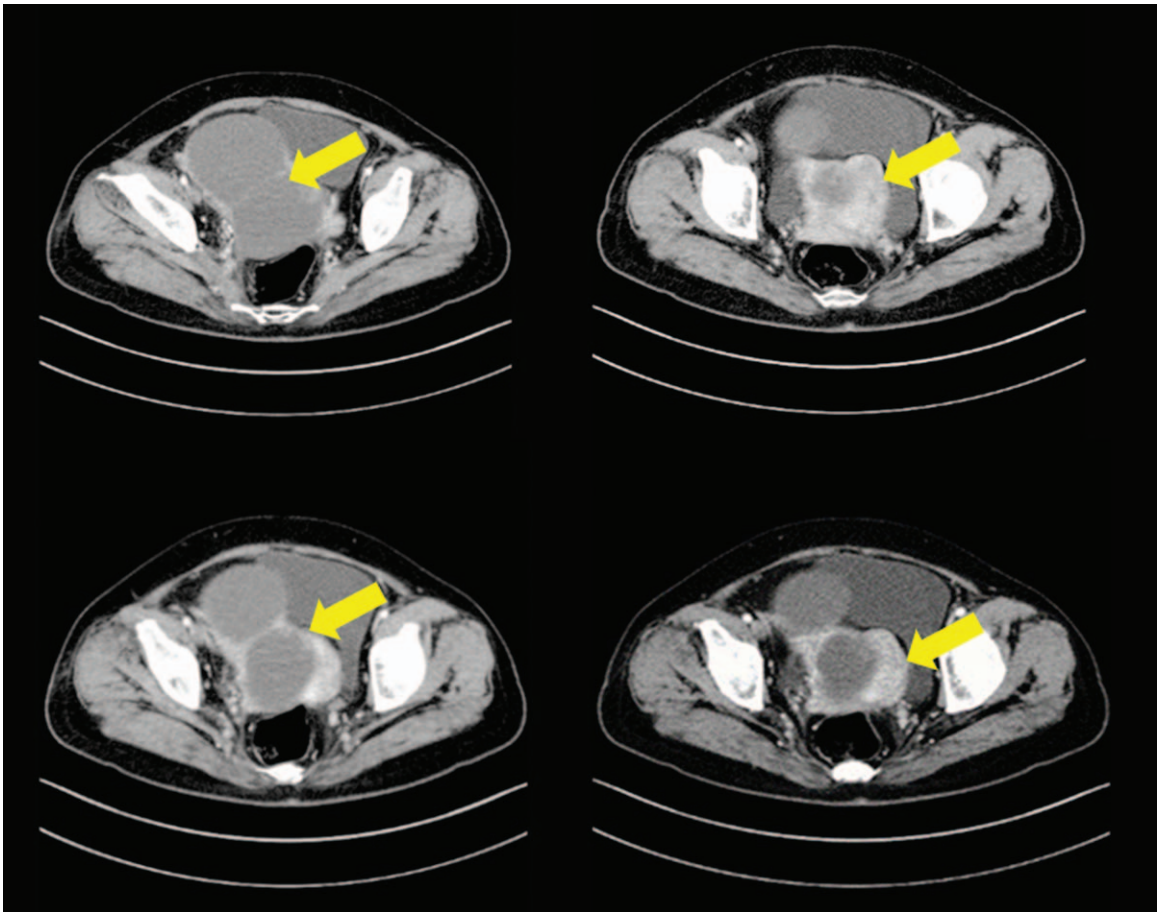

Figure 3. Case 2: Preoperative computed tomography images.

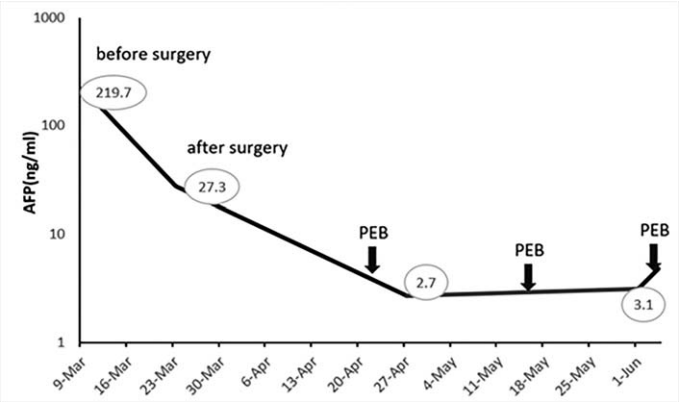

Figure 5. Case 2: Changes in serum a-fetoprotein (AFP) levels during chemotherapy. PEB = cisplatin, etoposide and bleomycin.

4. Discussion

The YSTs are the second most common ovarian germ cell malignancy, following dysgerminoma. They usually occur in childhood, adolescence, and early adult life, and are extremely rare in perimenopausal and postmenopausal female. Older patients may have different clinicopathologic features and prognosis compared with younger patients. Here, we reported 3 cases diagnosed and treated in Peking Union Medical College Hospital and reviewed the previous cases reported in English literature.

There are 55 cases reported in the previous literature. Their clinical features are listed in Table 2. The average age of onset was 62.5 years (range: 48–86). Because serum AFP was not routinely tested in postmenopausal women, the preoperative diagnosis of YST component in this population was quite difficult. The preoperative level of serum AFP was elevated in

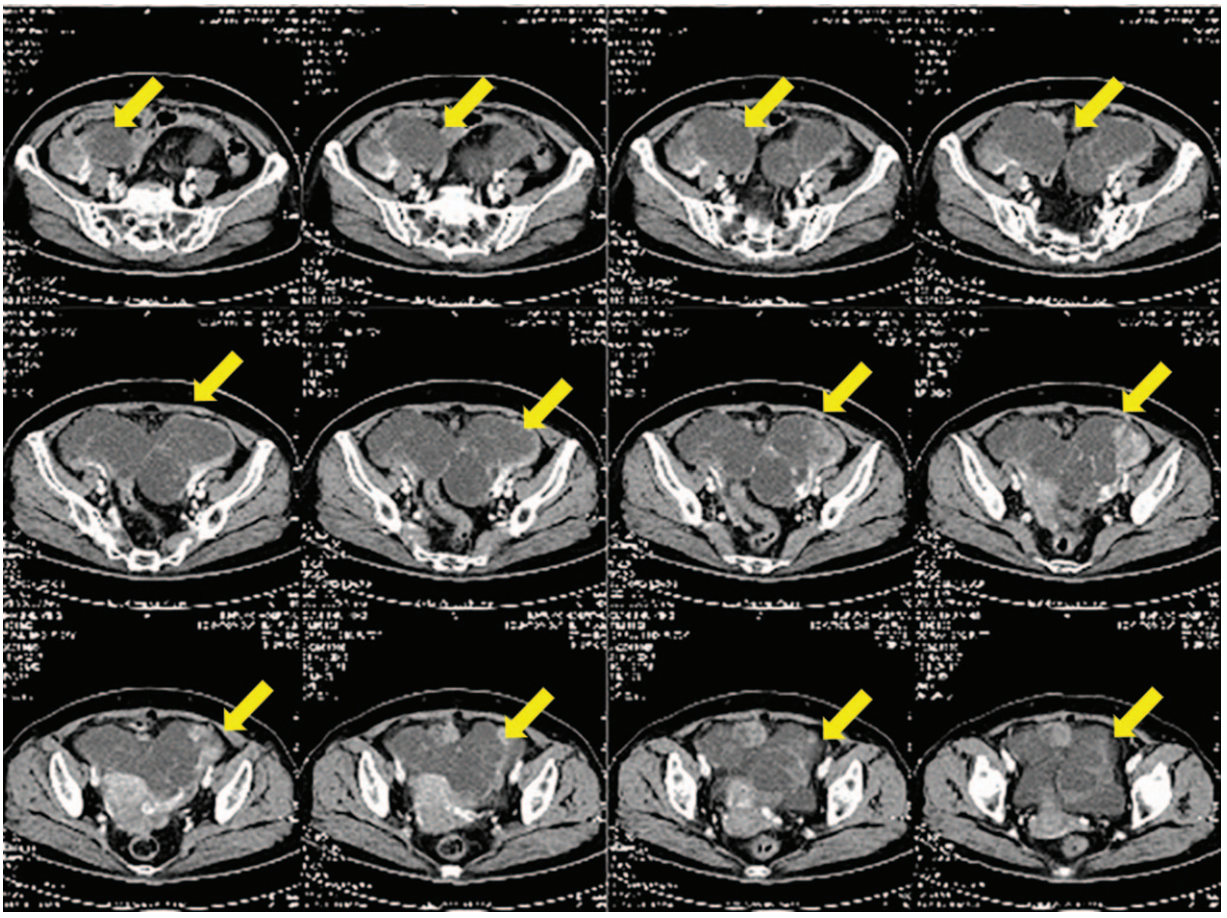

Figure 6. Case 3: Preoperative computed tomography images.

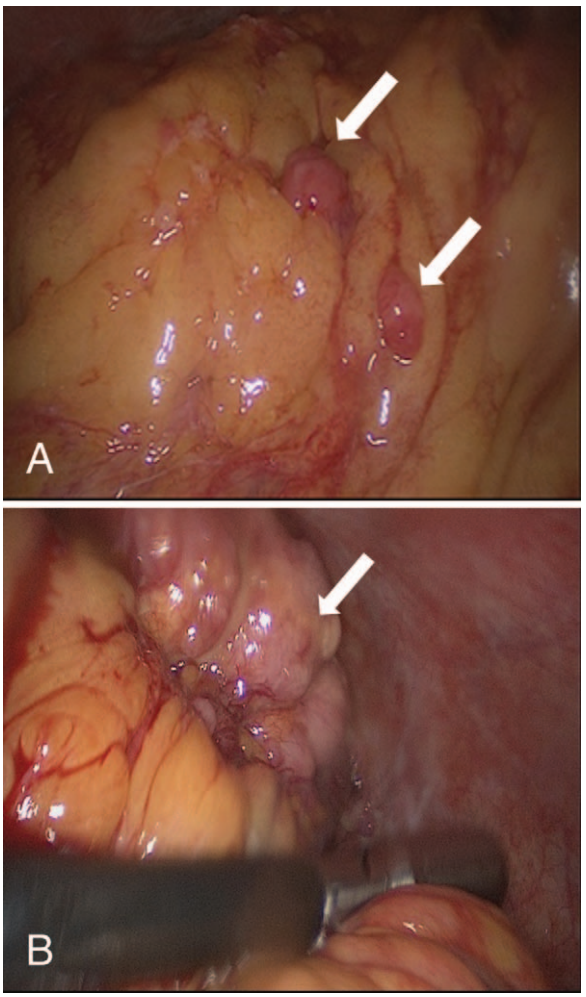

Figure 7. Images in laparoscopic exploration. (A) Metastatic nodules scattered in the omentum. (B) The right annexa was wrapped by omentum.

27 cases,[3,8,10–18,20–22,24,26–28,30] only 4 cases of AFP was normal,[6,11,26] the remaining was unknown.[4,5,7,9,11,19,23,25,26,29–31] Among 3 cases we reported, available serum AFP levels of 2 patients were both elevated, and the serum AFP level of the 3rd case was elevated significantly when testing after 1 cycle of chemotherapy.

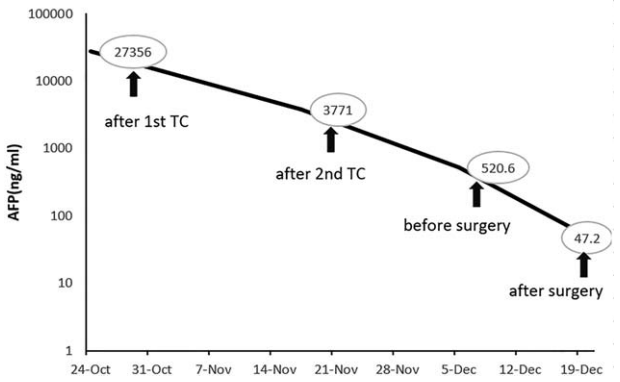

Figure 8. Case3: Changes in serum a-fetoprotein (AFP) levels during chemotherapy and surgery.

The YST can be pure or mixed with other germ-cell or epithelial tumors. As was seen in our cases, 3 postmenopausal women with YSTs all presented with a coexisting epithelial component and 1 case possessed 2 types of germ-cell tumors and epithelial components. In all previous cases, 20 were histologically classified as pure YST and 35 were mixed with other histologic components. The most common mixed component were endometrioid adenocarcinoma[6,11,13,16,18,20,21,24,25,30,31] and serous adenocarcinoma,[12,21,23,25,27,29,30] and other components included clear cell carcinoma,[21,27,30] carcinosarcoma,[11] embryonal carcinoma,[10] malignant mixed Müllerian tumor,[19] and so on. The differential diagnosis of ovarian YST in elderly patients is difficult, and the presence of mixed components adds difficulty to it. Especially when the YST component is limited, it can be overlooked. Due to the existence of the inherent heterogeneity of this tumor, adequate sampling is very important for a comprehensive and accurate diagnosis.

Although OGCTs are characterized by high malignancy, they are curable by surgery and combination chemotherapy. PEB chemotherapy is the most commonly recommended first-line chemotherapy regimen. For patients with malignant OGCTs receiving cisplatin-based first-line chemotherapy, the 5-year survival rate is close to 90%.[32] The cure rates for patients with early stage approach 100%, and even in patients with advanced stage, the cure rates are reportedly at least 75%.[33]

Interestingly, the simultaneous presence of YST and ovarian malignant epithelial tumor may herald a more aggressive behavior regardless of the stage of presentation.[21] The exact explanation of this biologic behavior is not yet clear. When malignant epithelial components and germ-cell tumors co-exists, the choice of which chemotherapy regimen is problematic. No ideal regimen has yet been established for this type of tumor. It has been hypothesized that the chemosensitivity of these tumor cells will differ from that of pure or mixed germ-cell tumors, since the yolk sac components of these tumors may originate from a different molecular pathway than do germ cell-tumors in younger patients.[21] Although the exact explanation for the pathogenesis of these tumor is unknown, 4 theories including the teratoma theory, retrodifferentiation, collision theory, and neometaplasia theory have been proposed.[6,16,18,30] Review of previous cases, 22 patients did not receive any chemotherapy or had no record for adjuvant therapy postoperatively. Among the 33 patients who received chemotherapy, 28 patients received platinum-based chemotherapy. Among 13 patients receiving PEB chemotherapy regimen, 2 patients[18,24] experienced disease progression during chemotherapy and 1 patient[24] experienced complete remission after changing to a second-line chemotherapy (docetaxel and carboplatin). She had been followed up for 48 months without sign of tumor recurrence.

Studies have shown that prognostic factors of ovarian YST includes tumor stage,[34] amount of ascites,[35] serum AFP decline rate,[35] residual tumor,[36] and chemotherapy regimen and chemotherapy course.[36,37] In premenopausal women, multivariate analysis showed that age was not a significant prognostic factor.[35] Due to the rarity of YST in postmenopausal women, whether age affects the prognosis has not yet been clear. Among the 55 patients reported in the literature, 28 were diagnosed as stage I or II, 16 stage III, and 2 stage IV. The stage of 9 patients were not available. The prognosis of OGCT in postmenopausal women is poor, even for patients with early-stage disease. Twenty-two of 46 patients with available staging were diagnosed with stage I disease,[6–8,11,13,14,16,18,20,21,26,27,29,30] but only 7 of them (32%) were alive for more than 20 months[7,16,20,21,26] with

Table 2

Summary of 55 postmenopausal patients with ovarian YSTs.

Case	Author	Year	Age	AFP, ng/mL	Surgery	Stage	Pathology	Chemotherapy	Outcome
1	Brown and Green[4]	1976	57	NA	TAH+BSO+Ometectomy	III	Pure YST	None	DOD: 3 mo
2	Ferracini et al[5]	1979	63	NA	TAH+Tumor debulking	NA	Pure YST	None	DOD: 2 d postoperatively
3	Rutgers et al[6]	1987	50	Normal	Primary: TAH+BSO After recurrence: omentectomy and peritoneal biopsies	IA	YST+EAC+EM	MOCy × 5 VP × 1 (after recurrence)	Recurrence: 8 mo, DOD: 8 mo
4	Mazur et al[7]	1988	82	NA	TAH+BSO+BPALN+Liver biopsy +Partial omentectomy	IA	YST+MC	NA	DF: 24 mo
5	Kinoshita[8]	1990	62	10,408.4	TAH+BSO	IA	Pure YST	EP × 2 PVP × 5	NA
6	Pliskow[9]	1993	54	NA	TAH, BSO+Omentectomy	NA	Pure YST	PEB × 3	DF: 24 mo
7	Kammerer-Doak et al[10]	1996	53	336	TAH, BSO+Omentectomy +Appendicectomy+Pelvic and para-aortic LN biopsy	NA	YST+Embryonal carcinoma	PEB × 3	DF: 60 mo
8	Nogales et al[11]	1996	71	Normal	TAH+BSO	IA	YST+EM+EAF	CBC × 6	DF: 12 mo
9	Nogales et al[11]	1996	64	>300	TAH+BSO	IA	YST+EAC	MOC × 3	Recurrence: 8 mo, DOD: 14 mo
10	Nogales et al[11]	1996	71	NA	TAH+BSO	III	YST+EM	CBC × 1	DOD: 3 mo
11	Nogales et al[11]	1996	73	23	TAH+BSO	III	YST+Carcinosarcoma	NA	DOD: 5 mo
12	Takizawa et al[12]	1996	69	18,100	BSO+Partial omentectomy	III	YST+Papillary serous carcinoma (peritoneum)	P × 2 (ip) followed by CAP × 6 Second line CaE × 2 due to biochemical recurrence	Recurrence: 18 mo, DOD: 24 mo
13	Horiuchi et al[13]	1998	53	2842.3	TAH+BSO+PLAN+Omentectomy	IA	YST+EAC	VPePMC × 6	Recurrence: 3 mo, DOD: 7 mo
14	Arai et al[14]	1999	71	55.6	TAH+BSO	IC	YST+MCA	EP	Recurrence: 3 mo DOD: 6 mo
15	Oh et al[15]	2001	75	17,318	TAH+BSO+Sigmoid colectomy with colorectal anastomosis, omentectomy, and pelvic node biopsy	IIIC	Pure YST	PE × 3	DOD: 4 mo, cardiac tamponade secondary to malignant pericardial effusion
16	Kamoi et al[16]	2002	54	13,143	TAH+BSO+Appendectomy and partial omentectomy	IC	YST+EAC	Ca (ip) followed by PeEP × 5	DF: 21 mo
17	Filiz et al[17]	2003	76	208	TAH+BSO+Infracolic omentectomy+Pelvic and para-aortic lymph node sampling	II	Pure YST	PEB × 4	Recurrence: 42 mo DOD: 48 mo
18	Lopez et al[18]	2003	51	37.1	TAH+BSO+Omentectomy	IC	YST+EAC+Mucinous cystadenoma+EM	PEB × 4	Persistent Progression DOD: 10 mo
19	Garcí a-Galvis et al[19]	2008	69	NA	Tumor debulking and omentectomy	IV	YST+MMT	None	DOD: 10 d postoperatively due to septic complications
20	Abe et al[20]	2008	52	24,518	TAH+BSO+PLN+PALN+Omentectomy	IC	YST+EAC	PEB × 3 TC × 3	DF: 20 mo
21	Roth et al[21]	2011	67	451,000	Partial omentectomy +Tumor debulking	IIIC	YST+LGSC	None	DOD: 10 d due to operative complications
22	Roth et al[21]	2011	48	200	TAH+BSO+Staging	IA	YST+EAC+CCC	5 cycles	DF: 24 mo
23	Roth et al[21]	2011	49	300	TAH+BSO+Omentectomy	IIIA	YST+CCC	TC	Recurrence: 3 mo DOD: 15 mo
24	Roth et al[21]	2011	60	2772		IC	Pure YST	TC × 2	DF: 14 mo

(*continued*)

Table 2

(continued).

Case	Author	Year	Age	AFP, ng/mL	Surgery	Stage	Pathology	Chemotherapy	Outcome
25	Lange et al[22]	2012	86	7010	TAH+BSO+Omentectomy +Appendicectomy+Lymph node sampling BSO+Omentectomy, pelvic peritoneal stripping+Left retroperitoneal tumor resection	IIIC	Pure YST	PEB × 4	NA
26	Varia et al[23]	2012	69	NA	NA	NA	YST+HGSC	NA	NA
27	Koi et al[24]	2014	56	374,700	TAH+BSO+PLN+Partial omentectomy, appendectomy, and partial peritonectomy	IIIC	YST+EAC+ EM	PEB × 2 (no response) Second-line: DC × 4 (AFP normal), DC × 2	DF: 48 mo
28	Roma and Przybycin[25]	2014	61	NA	TAH+BSO+Staging biopsies	NA	YST+HGSC+EAC	(ip) × 6	Recurrence: 7 mo, Under chemotherapy
29	Roma and Przybycin[25]	2014	70	NA	TAH+BSO+Staging biopsies	NA	Pure YST	6 cycles	Recurrence: 7 mo, under chemotherapy
30	Wang et al[26]	2014	60	16331	BSO+PLN+Omentectomy+Tumor debulking	IIC	Pure YST	PEB × 4	DF: 40.6 mo
31	Wang et al[26]	2014	53	1.67	TAH+BSO+Omentectomy+Dixon	IIB	YST+ADC	PEB × 3 After recurrence: TP × 2, DTP × 1	Recurrence: 3 mo DOD: 14.5 mo
32	Wang et al[26]	2014	55	4722	TAH+BSO+BPLND+OMNTC	IIC	Pure YST	PEB × 5 After recurrence: TC × 1	Recurrence: 8.5 mo DOD: 18.5 mo
33	Wang et al[26]	2014	55	14.42	TAH+BSO+OMNTC	IC	Pure YST	PEB × 6 After Recurrence: TP# × 1, TIP × 2 IrP × 3, PLDT × 1	Relapse: 9 mo DOD: 30.8 mo
34	Wang et al[26]	2014	50	NA	TAH+BSO	NA	Pure YST	DDP × 3, FP × 1 Persistent existence AHP × 1	Progression during chemotherapy DOD: 8.5 mo
35	Chen and Chen[27]	2014	61	11,233	TAH+BSO+Omentectomy +Appendectomy+PLN+PALN	IC	YST+CCA+HGSC	TC × 6	NA
36	Parker et al[28]	2015	60	11,677	Right hemi-colectomy, resection of the terminal ileum and cecum with ileostomy and mucus fistula formation	III	Pure YST	EP × 2 POMB–ACE	Recurrence: 17 d postoperatively but remains Under follow-up
37	Boussios et al[3]	2015	67	31,014 postoperatively	TAH+BSO+PLN+Appendectomy +Partial omentectomy and peritonectomy	NA	Pure YST	TC × 1 PEB × 1 TG × 1 CG × 1	DOD: 12 mo
38	Boussios et al[3]	2015	59	57 postoperatively	TAH+BSO+Omentectomy +Appendectomy	II	YST+Neuroendocrine tumor	Primary: None After recurrence: EP × 3	Recurrence: 12 mo DOD: 21 mo
39	McCarthy et al[29]	2016	62	NA	TAH+BSO+Staging (pelvic washings and omental biopsies)	IC3	YST+HGSC	Chemotherapy	NA
40	McNamee et al[30]	2016	69	NA	NA	IIIC	YST+HGSC	NA	NA
41	McNamee et al[30]	2016	59	Elevated	NA	IIB	YST+Large cell neuroendocrine	NA	DOD: 21 mo
42	McNamee et al[30]	2016	48	NA	NA	IIIC	YST+CCC	NA	DOD: 12 mo

(*continued*)

Table 2

(continued).

Case	Author	Year	Age	AFP, ng/mL	Surgery	Stage	Pathology	Chemotherapy	Outcome
43	McNamee et al[30]	2016	64	NA	NA	IIIA	YST+HGSC	NA	NA
44	McNamee et al[30]	2016	79	NA	NA	IA	YST+Borderline clear cell adenofibroma	NA	DF: 21 mo
45	McNamee et al[30]	2016	63	NA	NA	IA	Pure YST	NA	NA
46	McNamee et al[30]	2016	50	NA	NA	IC	Pure YST	NA	DF: 22 mo
47	McNamee et al[30]	2016	60	NA	NA	IC	Pure YST	NA	NA
48	McNamee et al[30]	2016	72	NA	NA	IC	IT, carcinoid tumor, EAC+YST	NA	NA
49	McNamee et al[30]	2016	56	NA	NA	IIIC	YST+HGSC	NA	DOD: 4 mo
50	McNamee et al[30]	2016	73	NA	NA	IC	YST+STIC	NA	NA
51	McNamee et al[30]	2016	62	555,000	NA	IIIC	HGSC+YST	NA	DOD: 20 mo
52	McNamee et al[30]	2016	73	NA	NA	IA	Pure YST	NA	NA
53	McNamee et al[30]	2016	68	NA	NA	IIIC	HGSC+YST	NA	RF: 1 mo
54	McNamee et al[30]	2016	63	Elevated	NA	IVB	YST+EAC	NA	DOD: 10 mo
55	Taranto et al[31]	2017	61	NA	TAH+BSO+Peritoneal biopsies +Peritoneal fluid analysis	NA	YST+EAC	TC × 6 Second line: CGBeT PEB × 4 EIP × 1 $P^{\#}G \times 1$ oral cyclophosphamide × 1	Recurrence: 24 mo DOD: 29 mo

ACE = actinomycin, cyclophosphamide, etoposide, AFP = a-fetoprotein, AHP = adriamycin, mechlorethamine, cisplatin, BPALN = biopsy of para-aortic lymph node, CBC = cisplatin-based chemotherapy, VP = cisplatin and vinblastine, CGBeT = carboplatin, gemcitabine bevacizumab, paclitaxel, DC = docetaxel and carboplatin, DF = disease free, DTP = docetaxel, nedaplatin, EAC = endometrioid adenocarcinoma, EAF = endometrioid adenofibroma, EIP = etoposide, ifosfamide, and cisplatin, EM = endometriosis, EP = cisplatin and ectoposide, FP = 5-Fu, cisplatin, HGSC = high-grade serous adenocarcinoma, IrP = irinotecan, nedaplatin, IT = immature teratoma, MC = mucinous cystadenofibroma, MCA = mucinous cystadenocarcinoma, MMT = malignant Müllerian mixed tumor, MOCy = vincristine, actinomycin D, and cyclophosphamide, NA = not available, NET = neuroendocrine tumor, $P^{\#}G$ = oxaliplatin and gemcitabine, PeEP = pepleomycin, etoposide and cisplatin, PEB = cisplatin, etoposide, and bleomycin, PLDT = pegylated liposomal doxorubicin, topotecan, POMB = methotrexate, vincristine, cisplatin, bleomycin, PVP = cisplatin, vinblastin, peplomycin, STIC = serous tubal intra-epithelial carcinoma, TC = paclitaxel, carboplatin, TG = paclitaxel, gemcitabine, TIP = paclitaxel, ifosfamide, oxaliplatin, $TP^{\#}$ = paclitaxel, oxaliplatin, TP = paclitaxel, cisplatin, VPePMC = vinblastine, pepleomycin, cisplatin, actinomycin D, and cyclophosphamide, YST = yolk sac tumor.

8 cases' survival information unavailable. Twenty-four died of the disease at a median time of 12.8 months after diagnosis and 13 patients still survived during follow-up. The longest follow-up time documented was 60 months.[10] Fourteen patients died of the disease within 1 year, although 5 patients had stage I or II disease with no residual tumor, and 3 of them received adjuvant chemotherapy with a PEB regimen. The recurrence time was documented in only 15 patients (median relapse time: 10.4 months [range: 1–42]), and only 3 of 15 patients with recurrence records were still under follow-up, and the others were all died (median additional survival time after recurrence: 7.3 months). After recurrence, no salvage surgery was reported before and most patients accepted platinum-based chemotherapy. The longest survival time after recurrence was 21.8 months.[26] The above data suggested that postmenopausal ovarian YST patients may have a poor prognosis compared with young patients.

Immunohistochemical staining of AFP is valuable for the histologic diagnosis of YST, while serum AFP levels contribute to the clinical diagnosis of YST and can help monitoring disease activity and chemotherapy response. Newer markers for YST including glypican-3 and SALL-like protein 4 (SALL4) may be useful in the identification of the YST component histologically. Glypican-3 (GLP3), which is an oncofetal protein expressed in fetal liver and malignant tumors of hepatocytic lineage, is more sensitive than AFP but not as specific.[11] Only AFP and GLP3 are used as YST characteristic immunopathologic markers that can be correlated with their corresponding serum levels.[38] SALL4 may be useful in differentiating YSTs areas originating in somatic tumors and also in the differential diagnosis with ovarian clear cell carcinoma.[39] All of our 3 cases showed diffuse strong expression of AFP and SALL4 in the YST component, supporting the diagnosis of YST. OCT3/4 is positive in dysgerminoma and embryonal carcinoma but negative in YST, as it was in our 3 cases. It should be noted that SALL4, AFP, and GLP3 co-expression in some gastric clear cell and hepatoid carcinomas.[40]

5. Conclusion

We reported 3 cases of mixed YST in postmenopausal females and as far as we know, we reported the first case of YST combined with both low-grade serous carcinoma and immature teratoma. Ovarian YSTs in postmenopausal women are characterized by high malignancy and may have a worse prognosis compared with those in younger patients. More active treatment is needed especially when mixed with epithelial cancer components. When YST and epithelial cancer components co-exist, YST components may be less responsive to traditional germ-cell tumor chemotherapy because of possible differentiation of epithelial components. Adjuvant chemotherapy should be selected to simultaneously target epithelial ovarian tumors and germ-cell tumors. Platinum-based chemotherapy is recommended.

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