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Case Report

Bilateral ovarian mixed epithelial adenocarcinoma in a postmenopausal woman with unilateral ovarian yolk sac tumor component

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Abstract: Ovarian yolk sac tumors (YSTs) usually occur in the young women and have been rarely documented in perimenopausal and postmenopausal women. The different age distribution supposes their complex nomenclature and histogenesis. We report a case of bilateral ovarian epithelial carcinoma with right ovarian YST component in a postmenopausal woman. The patient was treated by surgery and adjuvant combination chemotherapy of taxol and carboplatin for 6 courses and has been clinically free of tumor for 6 months. The correlation between the YST and the epithelial components always confuse us. Ovarian yolk sac tumors are not a discrete entity and represent a multifaceted group of neoplasms. The conjunction of multi antibodies help in differential diagnoses. In addition to a thorough case description, the literature concerning this entity is reviewed and discussed.

Keywords: Yolk sac tumor, the mixed epithelial adenocarcinoma, SALL4, GPC-3, PAX8, postmenopausal women

Introduction

Yolk sac tumor (YST) or endodermal sinus tumor is a malignant germ cell tumor characterized by endodermal differentiation, which typically occurs in children and young women (average 19) [1], either in combination with other components in mixed germ cell tumor or in a pure form [2]. However, YSTs in perimenopausal and postmenopausal women are exceedingly rare; especially combination with a surface epithelial-stromal tumor. Furthermore, unlike pure yolk sac tumor, these tumors are much more aggressive and are associated with a very poor prognosis, whether or not an epithelial component is detected [3].

Recently, reports indicated that SALL4, glypican3 (GPC-3) and PAX8 were the novel markers in the differential diagnosis between YST and epithelial carcinoma, such as endometrioid and clear cell adenocarcinoma [4, 5] on account of SALL4 and GPC-3 for the better immunochemical expression modes (nuclear, membrane and cytoplasm respectively), sensitivity and specificity than AFP. SALL4 expresses consistently in YST and most other germ cell tumors 6. GPC-3 is expressed in fetal tissues and trophoblastic cells and has been reported in YST, more often than in clear cell adenocarcinoma [6]. On the contrary, PAX8 is a transcription factor essential for organogenesis of the thyroid, kidney and Müllerian system, which associated with Müllerian surface epithelium tumors, and negative in the ovarian germ cell tumors [7].

We herein describe a case of an unusual and extremely rare bilateral ovarian mixture high-grade serous carcinoma with components of YST and clear cell adenocarcinoma in a 61-year-old postmenopausal woman involving the right ovary, and provide a review of the literature. As far as we know, such a combination has not been described before in the literature, although a single case of pure low grade serous carcinoma, a distinct tumor type from high grade serous carcinoma, associated with YST has been reported. Postoperatively, the patient was treated an adjuvant combination chemotherapy of taxol and carboplatin for 6 courses.

Case report

Clinical information

A 61-year-old female, gravid 2, para 2, presented with abdominal distention of half a month's duration. Pelvic ultrasound examination showed a large complex cystic-solid mass on the bilateral adnexa respectively with a clinical diagnosis of ovarian cancer. Computerized tomographic scan confirmed these findings by showing an 18.1×13.2×10.5 cm irregular pelvic mass on the right adnexa, and a 7.4×5.4×5.4 cm mass on the left adnexa. The preoperative tumor markers showed an elevated serum AFP level of 11233.0 ng/ml (normal value < 15.0 ng/ml), CEA 206.4 ng/ml (normal value < 5.0 ng/ml), CA125 773.2 U/ml (normal value < 35.0 U/ml), CA153 391 U/ml (normal value < 25.0 U/ml), respectively. The other tumor markers CA199, SCC and the serum human chorionic gonadotropih (β-HCG) were in normal range.

The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, appendectomy, pelvic lymphadenectomy and para-aortic lymphadenectomy. There was ascitic fluid in the abdominal and pelvic cavity. The right ovary was replaced by a large multilocular mass with a smooth external surface except for a split. The surgery was optimal, that is, all gross tumors were resected almost completely. And the examination of ascitic fluid was negative. Her FIGO stage was IC.

After the operation, the serum level of these tumor markers declined rapidly and remarkably. On the fifteenth postoperative day, AFP was 1482.0 ng/ml; CEA was 59.9 ng/ml; CA-125 210.0 U/ml. After the 6th course chemotherapy, her AFP, CEA and CA125 levels normalized to 5.0 ng/m, 9.7 U/ml and 15.2 U/ml, respectively.

Pathology findings and immunohistochemistry

On macroscopic examination, the right ovarian tumor measured 18.1×13.2×10.5 cm. The sectioned surface was solid and cystic, spongy, pale yellow, with partly hemorrhagic and necrotic change. The left ovary was replaced totally by the tumor, 7.4×5.4×5.4 cm in size, cystic-solid with gray-yellow cutting face, which had a largely smooth outer surface and an inner lining with friable papillary excrescences. The uterus, the bilateral fallopian tubes, cervix and momentums were grossly and histological unremarkable.

Histopathology examination showed that there was typically high-grade serous carcinoma in the left tumor, with characteristic papillary architecture with the papillae, secondary and even tertiary papillary processes and prominent atypical cells.

The histopathological findings of the right ovarian tumor were much more complex after extensively sampled (35 paraffin blocks), 70% of the primary neoplasm was YST and 30% was epithelial components. The epithelial component was composed of a mixture of papillary high-grade serous carcinoma (20%) and clear cell adenocarcinoma (10%) component. The YST component showed predominantly a meshwork micro cystic (reticular) pattern in some areas primitive intestinal patterns were also noted, showing the twisted glands lined by the moderate to severe atypical epithelial cells with prominent goblet cell. Eosinophilic (hyaline) bodies were scattered throughout the reticular and primitive intestinal patterns. And the hepatoid patterns were also noticed. These constructions were considered to be YST, and the immnohistochemical staining for AFP, SALL4, and GPC-3 were also positive, in support of this diagnosis. Furthermore, there were areas interpreted as endometrioid-like variant of YST that were extremely difficult to differentiate from an endometrioid adenocarcinoma morphologically, as they had gland-like spaces, which were lined by tall columnar cells with extensive apical and subnuclear or supranuclear vacuoles. The immnohistochemical staining patterns suggested that these areas were not an endometrioid adenocarcinoma but an endometrioid variant of YST, in light of the positivity of AFP, SALL4 and GPC-3, and the negativity of PAX8, CK7 and EMA.

The right ovarian epithelial components were composed of a mixture of high-grade serous adenocarcinoma and minor clear cell carcinoma, where the immnohistochemical staining were performed and revealed strong, diffuse, nuclear positivity for P53, Ki67, ER and cytoplasm for PAX8, EMA and CK7, whereas absent for SALL4, AFP and GPC-3. However, there were also some special areas displayed sheets of

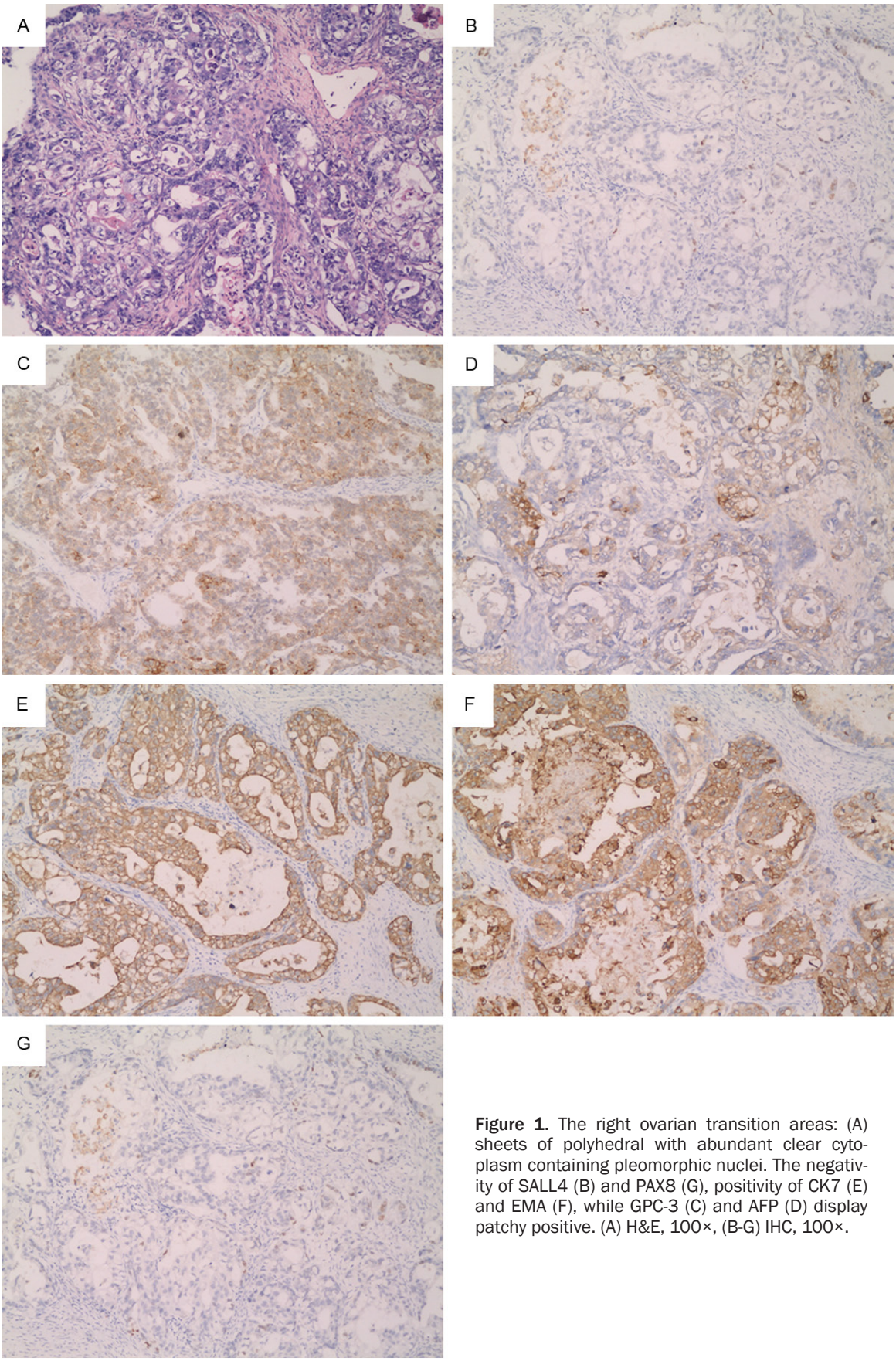

Figure 1. The right ovarian transition areas: (A) sheets of polyhedral with abundant clear cytoplasm containing pleomorphic nuclei. The negativity of SALL4 (B) and PAX8 (G), positivity of CK7 (E) and EMA (F), while GPC-3 (C) and AFP (D) display patchy positive. (A) H&E, 100×, (B-G) IHC, 100×.

Table 1. Cases of yolk sac tumor associated with ovarian epithelial tumors

Cases	No. Reference	Age	Diagnosis	FIGO stage	Serum AFP (ng/ml)	Chemo-therapy	Endome-triosis	Follow-up
Rutgers et al. [8]	1987	50	EAC, YST	IC	720	YES	EC	DOD 8 mos
Nogales et al. [9]	1996 C1	64	EAC, YST	IA	> 300	YES	EC	DOD 14 mos
	C2	71	EAC, EAF, YST	IA	Negative	YES	NO	Alive 12 mos
	C3	31	EAC, YST	III	7600	YES	EC	DOD 8 mos
	C4	71	EAC, YST	III	ND	YES	NO	DOD 3 mos
	C5	40	EAC, YST	IV	33	YES	NO	DOD 5 mos
	C6	73	MMMT, YST	III	23	YES	NO	DOD 14 mos
Mazur et al. [14]	1996	82	MCAF, YST	IA	ND	NO	NO	Alive 2 yrs
Horiuchi et al. [12]	1998	53	EAC, YST	IC	2842	YES	EC	DOD 6 mos
Arai et al. [15]	1999	71	MC, YST	IC	55.6	YES	NO	DOD 7 mos
Kamoi et al. [13]		54	EAC, YST	IC	13.143	YES	EC	Alive 21 mon
Lopez et al. [11]	2003	51	EAC, MCA, YST	III	720	YES	AE	DOD 10 mos
Mc Bee et al. [16]	2007	41	EAC, UC, YST	III	259	YES	NO	DOD 12 mos
Garcia-Galuis et al. [17]		69	MMMT, YST	IV	ND	NO	NO	DOD 0.3 mos
Abe et al. [18]	2008	52	EAC, YST	IA	24.518	YES	NO	Alive 20
Roth et al. [10]	2011 C1	67	LGSC, YST	IIIC	> 51.000	YES	NO	DOD 0.3 mos
	C2	48	EAC, CCAC, YST	IA	200	YES	EC	Alive 2 yrs
	C3	49	CCAC, YST	IIIA	300	YES	NO	DOD 15 mos
Varia et al. [19]	2012	69	SC, YST	ND	ND	NO	NO	Not mentioned
Roma et al. [6]	2014 C1	61	SC, EAC, YST	ND	ND	YES	EC	Recu 7 mos
Present case	2014	61	SC, CCAC, YST	IC	11,233	YES	NO	Alive 6 mos

AE, atypical endometriosis; CCAC, clear cell adenocarcinoma; EAC, endometrioid adenocarcinoma; EAF, endometrioid adenofibroma; EC, endometriotic cyst; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; MCA, mucinous cystadenoma; MCAF, mucinous cystadenofibroma; MMMT, malignant Mullerian mixed tumor; ND, not done; UC, undifferentiated carcinoma; YST, yolk sac tumor.

polyhedral with abundant clear cytoplasm separated by dedicated fibro vascular septa, containing large, highly pleomorphic nuclei, without conspicuous hobnail cells, were interpreted as transition areas that have the intermediate characteristic between epithelial malignancy and germ cell tumor conformed by the immunostainning results (**Figure 1A-G**).

The contra lateral fallopian tubes and uterus were unremarkable. The pelvic and para-aortic lymph nodes were free of tumor, and there was no endometriosis in the resected organs except adenomyosis. Endometrium was atrophic and unremarkable.

Discussion

In 1987, Rutgers et al [8] reported the first case of ovarian epithelial cancer associated with YST in postmenopausal women and the patient's age ranged same as epithelial ovarian carcinoma (average 53) [9]. On the contrary, YST usually occurs in young girls (average 19). The bimodal age distribution of patients with ovarian YST suggests different histogenetic mechanisms of tumor in the two age groups.

To the best of our knowledge, including our case, a total of 21 cases of ovarian epithelial neoplasm associated with YST in perimenopausal or postmenopausal women have been documented in literature and in 2 of them, the ovarian epithelial component was entirely benign [9, 10]. The clinical features and histological finding of these cases are summerarized in **Table 1**. The 21 cases displaying a combination of YST and epithelial tumor are as follows: 13 endometriod carcinoma (65%), 2 clear cell adenocarcinoma, 2 MMMT, 2 mucinous cystadenoma and cystadempfibroma, 1 mucinous adenocarcinoma, 2 serious adenocarcinomas and 1 undifferentiated carcinoma. The combinations of multi-ovarian epithelial components were the commonest form. The most common reported epithelial component was endometrioid

carcinoma, which is known to be associated with endometriotic cyst in 7 cases; another one endometriotic cyst was connected with serious adenocarcinoma. The mixture epithelial carcinoma of serous carcinoma and clear cell carcinoma components associated with YST in our own case was never documented before.

As is well known, the serous carcinoma often involves the bilateral ovaries in almost two-thirds of all cases. As YSTs component merely existing in the right ovary and the bilateral ovarian involved by the epithelial component in our own, the epithelial ovarian tumor origin should have a bit more supportive. Four theories including the teratoma theory, retro differentiation, collision theory and neometaplasia theory have been reported [1, 2]. As far as the histogenesis was concerned, the YSTs component was speculated by a molecular pathway totally different from those occurring at an earlier age, although the exact explanation for this biologic behavior was not yet been elucidated. It has been suggested that somatic carcinomas have the ability to acquire a germ cell differentiation, and the germ cell component is thought to derive from somatic mesodermal cells, and not from germ cells [9, 12, 13], owing to germ cells not identified histological in the ovaries of perimenopausal or postmenopausal women. Moreover, on one hand, the IHC results in our own results showed there were indeed transition areas (positive for GPC-3, AFP, CK7 and EMA, while absent for SALL4 and PAX8), which means possessing the characteristics of germ cell and epithelial cell differentiation in the meantime. Previously, Meguro et al [20] and Morimoto et al [21] also reported AFP-producing ovarian epithelial adenocarcinoma with showing germ cell differentiation in postmenopausal woman, which were categorized as an intermediate entity between epithelial malignancy and germ cell tumor. On the other hand, there was ovarian epithelial carcinoma companied by the elevated serum AFP levels and positive immunoreactivity for AFP [22-24]. Therefore, these phenomena could only be explained by a retrodiffrentiation of neometaplastic process, which appears to be the most reasonable theory to explain the histogenesis of this tumor. we believe that the surface epithelial tumor with YST components in perimenopausal and postmenopausal women, constitute a single entity that is distinct from YSTs (germ cell origin) in younger patients, and the chemosensivity of these neoplastic cells would be different from those cells of pure or mixed germ cell tumors.

Herein, we also should keep our eyes on some cases that the pure ovarian YST in premenopausal and postmenopausal women. So far, another 8 cases were reported in documents of pure YST without any ovarian epithelial tumor components in perimenopausal and postmenopausal women [6, 25-31], and one of them specifically coexisted with endometriosis [6]. As for this phenomenon, it was a reasonable explanation that the epithelial ovarian carcinomas components totally transformed to YST, in which the epithelial components were not detected or were overgrown. Roma et.al had reported pure YSTs in a postmenopausal woman adjacent to areas of endometriosis in the same ovary and prompted the hypothesis that YST could develop directly from the endometriotic cyst, having nothing to do with epithelial tumors [6]. Perhaps this is another alternative reasonable explanation.

YST exhibits a wide range of histological patterns that include: micro cystic or reticular, endodermal sinus, solid, alveolar-glandular, polyvesicular vitelline, myxomatous, papillary, macrocystic, hepatoid and glandular. Some of these patterns may resemble other types of ovarian epithelial tumors and cause difficulties in diagnosis. In our own case, the YST component showed predominantly reticular pattern, and the primitive intestinal patterns with prominent goblet cell and the hepatoid patterns were also notable, without typical Schiller-Duval body. The diagnosis of YST is supported by displaying clear and strong immunhistoochemical positive for AFP, SALL4, and GPC-3 (cytoplasm, nuclear, cytoplasm and membrane, respectively), while the CK7, PAX-8 and EMA (positive in clear cell adenocarcinoma and endometrioid carcinoma, but not in YST [32, 33] were negative or weakly positive patchily. There were also areas were extremely difficult to differentiate from an endometrioid adenocarcinoma morphologically. The IHC staining patterns suggested that these areas were not an endometrioid adenocarcinoma but an endometrioid variant of YST, due to the positivity for AFP, SALL4 and GPC-3, and absent for PAX8, CK7 and EMA. There were also areas that expressed AFP, SALL4, GPC-3, CK7 and EMA at the same time; it was sup-

posed to be an intermediated situation between YST and epithelial malignancy. Moreover, the differentiation between YST and clear cell adenocarcinoma sometimes was really difficult for the solid, tubulocystic areas in our own. These areas showed diffusely and strongly positive for CK7 and EMA and negative for SALL4, GPC-3 and AFP (although GPC-3 and AFP focally and weakly positive), while the PAX8 was absent, which was different from the report of Roma et al [6]. However, we prefer the diagnosis of the clear cell adenocarcinoma, for the morphological pattern and the presence of CK7-EMA positive34 and SALL4-GPC-3-AFP negative. Therefore, the conjunction of multi antibodies especially the germ cell indicators, such as SALL4, GPC-3 and AFP, and the epithelial tumor indicators of PAX-8, CK7 and EMA appears to be very important in differential diagnosis for the morphological overlap.

Serum AFP is not a routine inspection item in elderly women before the operation. Of all the cases in documents, preoperative serum AFP elevation was proven in 15/21 cases. Epithelial ovarian carcinoma rare secretes AFP especially in postmenopausal women. In our case, the serum AFP level decreased rapidly after the operation and went down along with the chemotherapy courses. Hence, AFP is a useful tumor marker for germ cell tumors of the ovary and is valuable for both diagnosis and follow-up.

Disclosure of conflict of interest

None.

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