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Case Report

Ovarian yolk sac tumor (YST) in a postmenopausal patient: case report and review of the literature

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Summary

Purpose: Report of one case of ovarian yolk sac tumor (YST) in a postmenopausal patient and review of the literature. *Materials and Methods:* The case the authors present is of a 77-year-old woman with ovarian YST along with a serous carcinoma and an endometriotic cyst component. They also review and summarize the findings of already reported cases. *Results:* Sixty cases of ovarian YSTs in postmenopausal patients have been described from 1976 to 2017, including the 23 found in the literature (PubMed and Elsevier) and the one reported in this article. The introduction of bleomycin/ etoposide/ cisplatin (BEP) chemotherapy for malignant germ cell tumors has improved outcomes in premenopausal women, but it does not have a similar impact on postmenopausal patients. *Conclusions:* The outcome for postmenopausal patients remains poor, even for those presenting with early stage disease or with pure YST. Further research is required to determine the pathogenesis and plan an effective therapy for this age group.

Key words: BEP; Malignant; Ovarian; Postmenopausal; Yolk sac tumor.

Introduction

Germ cell tumors account for 20-30% of ovarian tumors. Almost 95% of them are benign cystic teratomas [1-4]. Yolk sac tumors (YST) represent the second most frequent (20-25%) germ cell tumors of the ovary (following dysgerminomas) and they comprise only 2-3% of ovarian cancers [1, 4-7]. Most ovarian YST occur in children and young women with a median age at presentation 19 years [2, 5, 8-9].

YST in peri- and post menopausal women are extremely rare and they are believed to arise from a molecular pathway different from those occurring in younger patients [3-4, 6, 8]. Ovarian YSTs usually occur as pure tumors, but they may also occur as part of a mixed germ cell tumor (usually coexisting with dysgerminoma). An association with an epithelial ovarian component (usually endometrioid carcinoma) rarely exists, but when it does it is most common in older patients [1-4, 8, 10- 11].

Case Report

The present patient is a 77-year-old woman (22 years post menopause) who presented with vaginal bleeding for the past four days. Ultrasound examination of the lower abdomen revealed that the endometrium was thickened up to 1.8 mm. A complex mass measuring 8.7×6.3 cm was found in association with the right ovary and the uterine fundus. No fluid was observed in the cul-de-sac.

The patient's past history included arterial hypertension, hypothyroidism, and hypercholesterolemia. She had undergone appendectomy and excision of an endocervical polyp (20 years ago).

The patient underwent diagnostic dilation and curettage. Microscopic examination of the endometrial curettings revealed atrophic endometrium and fragments of a benign endometrial polyp. Further imaging examination was performed. Computerized axial tomography (CAT) scan of the upper and lower abdomen showed: a mass measuring 14×13×11 cm, with solid and cystic components, which seemed to originate from the right parametrium. Ascites was also present. CAT scan of the thorax showed substernal goiter and bilateral pleural effusions. The preoperative blood tests showed: AFP = 1175.15 ng/ml, CEA = 102.57 ng/ml, CA19-9 = 199.54 U/ml, CA15.3 = 59.2 U/ml, CA125 = 242.7 U/ml, and SCC = 2.4ng/ml. Cytology of the ascitic fluid showed malignant cells consistent with metastatic adenocarcinoma (Figure 1, 2). Laparotomy with right salpingo-oophorectomy and peritoneal biopsies were performed.

The right salpingo-oophorectomy specimen consisted of a well-circumscribed tumor, partially encapsulated. Capsular tears were noted focally. The tumor measured 11cm in diameter. Its cut surface was solid and partially cystic with haemorrhagic contents. Areas of necrosis were also noted. A peritoneal biopsy measuring 2 cm in diameter was also submitted for pathologic evaluation.

Microscopic examination showed that the solid areas of the neoplasm consisted of proliferating small glands with subnuclear epithelial vacuoles lying within an ovarian type stroma (Figure 3). Other areas showed tubular, papillary formations. Some areas

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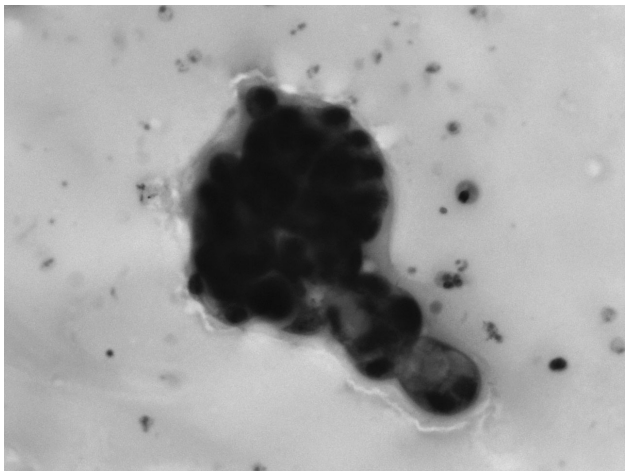

Figure 1. — Cytologic preparation Papanicolaou stain ×400. Cluster of neoplastic cells.

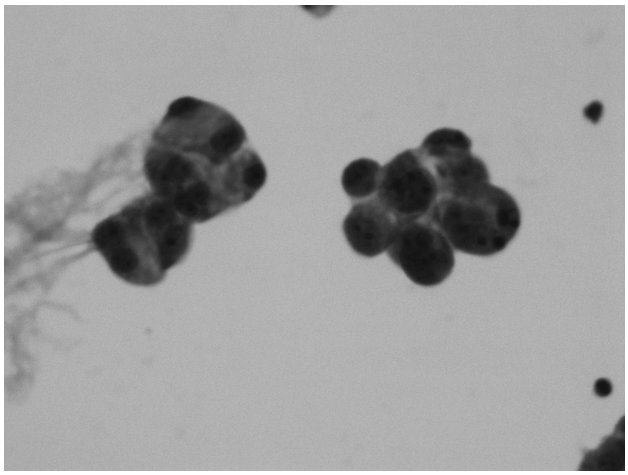

Figure 2. — Thin Prep Papanicolaou stain ×400. Clusters of neoplastic cells.

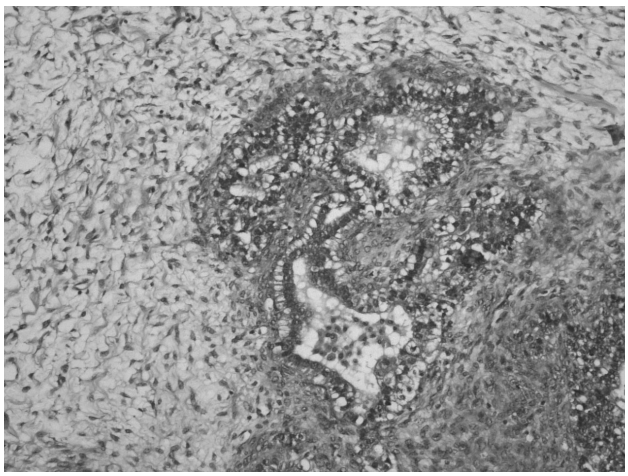

Figure 3. — Solid area with glands with subnuclear epithelial vacuoles within ovarian type stroma ×100.

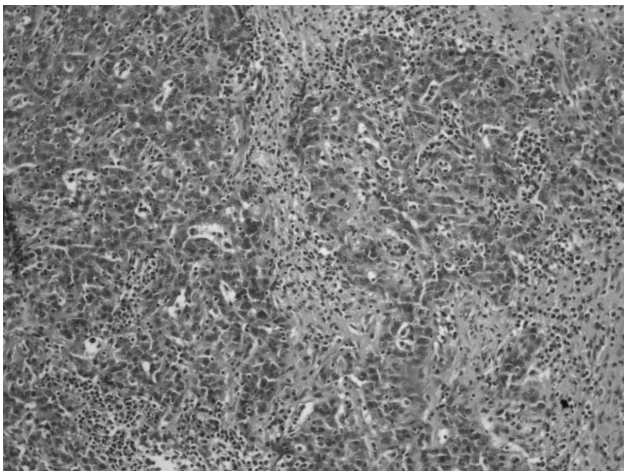

Figure 4. — Solid growth pattern of neoplastic cells with focal glandular differentiation ×100.

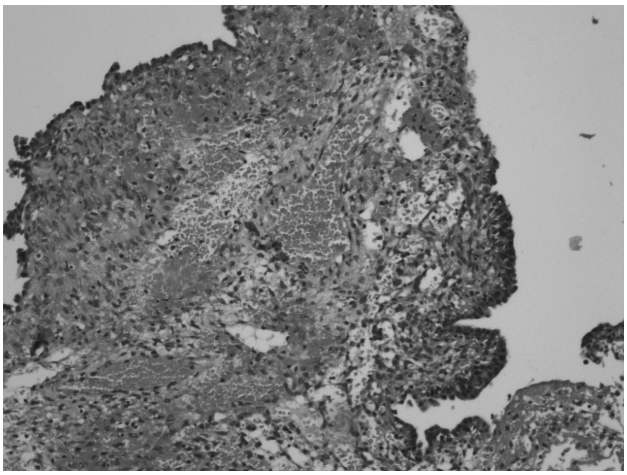

Figure 5. — Well-differentiated epithelium and subepithelial endometrial type stroma consistent with endometriotic cyst ×100.

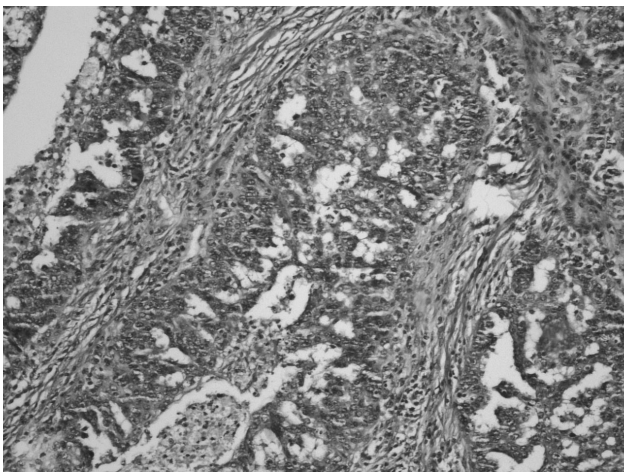

Figure 6. — Neoplastic area resembling serous ovarian carcinoma ×100.

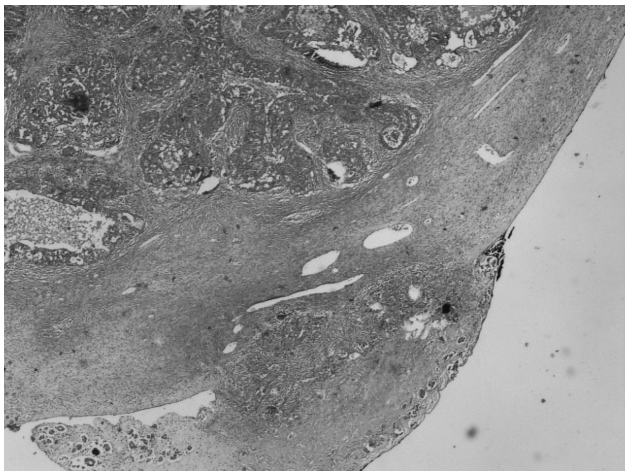

Figure 7. — Tumor implant at the ovarian surface ×20.

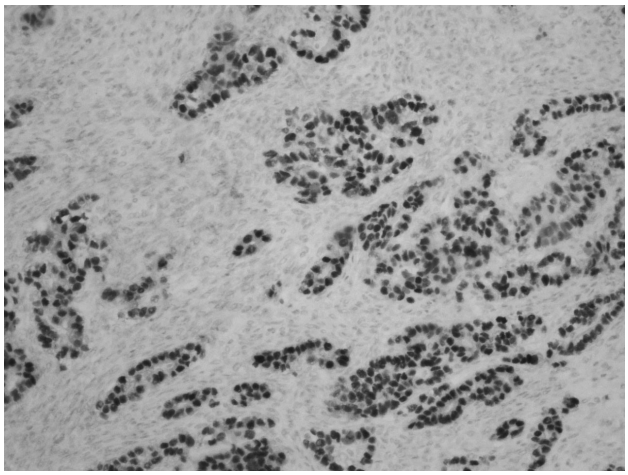

Figure 8. — CDX2 positive in glandular tumor areas ×100.

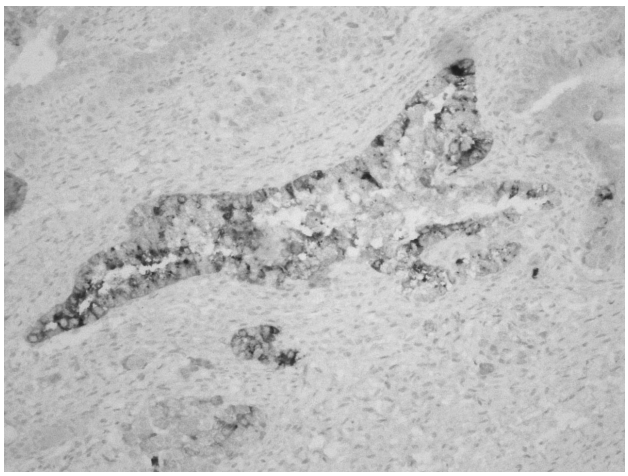

Figure 9. — AFP positive in glandular component of the tumor ×100.

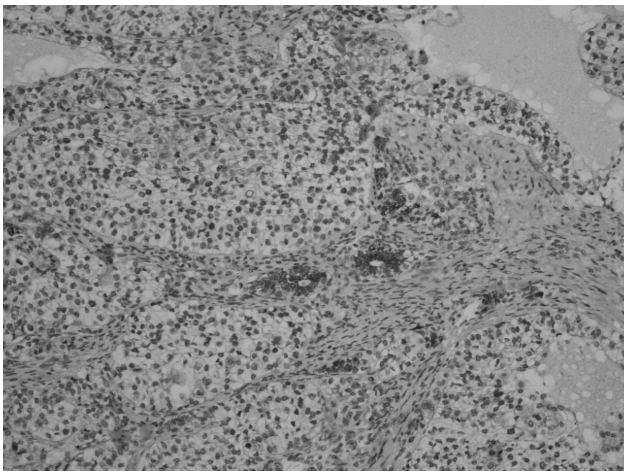

Figure 10. — HepPar positive in glandular and negative in solid component of tumor ×100.

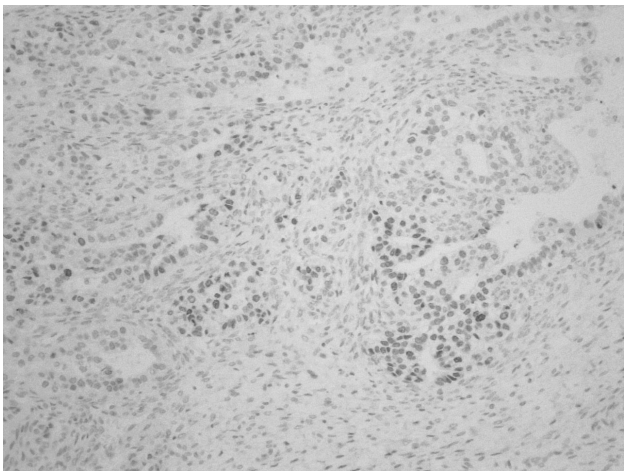

Figure 11. — SALL-4 positive in glandular component of tumor ×100.

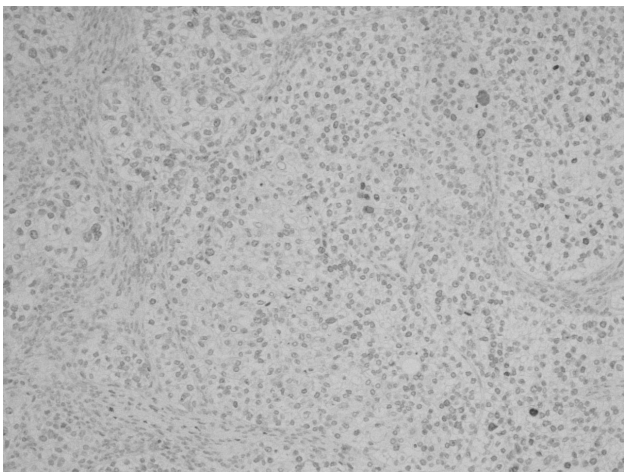

Figure 12. — SALL-4 focally positive in solid component of tumor ×100.

consisted of cystically dilated glands with central necrosis. Finally, in other areas the neoplastic cells had a solid growth pattern, with focal glandular differentiation (Figure 4).

The cystic spaces were lined by well differentiated epithelium. In a few cystic lesions, subepithelial endometrial type stroma was identified and consistent with endometriotic cyst (Figure 5). Finally, in some areas the neoplasm had the appearance of endometrioid and serous ovarian carcinoma (Figures 6 and 7).

The differential diagnoses considered were metastatic carcinoma (large intestine), ovarian epithelial carcinoma (e.g. endometrioid, serous), and ovarian YST. In view of the elevated levels of serum AFP, it was felt that ovarian yolk sac tumor was the most likely diagnosis.

Immunohistochemistry was performed with the following results in the solid areas of the tumor with glandular differentiation or in the small glandular areas of the tumor: the neoplastic cells were negative for CK7, CK20, WT-1, PAX8, Vimentin, CA19-9, and ER. P53, p16, and CDX2 were strongly positive (Figure 8). PgR, AFP, CEA, EMA, HepPar, and CK18 were positive in the glandular component and negative in the solid component of the tumor (Figures 9 and 10). Chromogranin and synaptophysin were diffusely positive in the tumor's glandular component. SALL4 immunostain was focally positive in the neoplastic cells (Figures 11 and 12). In the areas of the tumor with endometrioid or serous morphology, the neoplastic cells were positive for ER, PgR, p53, and negative for Vimentin. WT-1 and p16 were positive with a cytoplasmic staining pattern. The morphology and immunohistochemical findings were compatible with YST of glandular (endodermal, somatic) type, in association with endometriotic cyst and serous carcinoma (Stage IC/T1cN0M0).

Postoperatively the levels of AFP, β-hCG, and LDH in peripheral blood were normal. The patient was treated with four cycles of etoposide and cisplatin and she is alive and free of disease at the moment. The peritoneal biopsy was adipose tissue with fibrosis and inflammation, without evidence of neoplastic disease.

Discussion

Ovarian YST are extremely rare in postmenopausal women and usually occur in association with surface epithelial tumors, in most cases of endometrioid type [1-4, 8, 12]. According to Boussios *et al.*, and taking into account their reported cases, 36 such tumors have been reported from 1976 [13] to 2015 [5-8, 10, 13-34]. After further search (PubMed and Elsevier), the present authors found four more cases of ovarian yolk sac tumors in postmenopausal patients reported during this period and 19 more during the past year (2016) [3, 11, 35-39] (Table 1).

These tumors present as a rapidly enlarging pelvic mass that causes abdominal distention and pain. Most of them are unilateral and may have metastases at presentation with local spread of the tumor throughout the peritoneum. Raised serum AFP levels are a characteristic finding for this type of ovarian tumor [6].

The pathogenesis of ovarian yolk sac tumors in postmenopausal women is not yet completely understood, but it is postulated that it differs from that in young adults. As germ cells are not histologically identifiable at the ovaries of postmenopausal women, and an association with an epithelial component is described in most of the reported cases, it is assumed that the YST component arises from the epithelial neoplasm, secondary to a process referred to as neometaplasia or retrodifferentiation [3, 4, 26, 27, 32, 39, 40]. Neometaplasia/retrodifferentiation is also called aberrant differentiation and refers to the ability of neoplastic cells for germ cell differentiation. In these carcinomas, the germ cell component is thought to be of somatic mesodermal origin [4, 29, 32, 39, 41]. Nogales *et al.* [40] also suggested that these YST may originate from pluripotent malignant stem cells present in the somatic tumor [30, 39, 40, 41]. As far as the microscopic appearance is concerned, numerous patterns of growth have been described and more than one are usually present in the same tumor [3, 4, 40]. The most common endodermal extraembryonal patterns are the reticular-microcystic, containing a network of anastomosing microcysts lined by flattened epithelium, and the endodermal-pseudopapillary pattern characterized by Schiller-Duval bodies. Rarely, parietal, polyvesicular and tubular patterns have been described. Areas that reproduce the histology of endodermal somatic derivatives may mimic other different tumors. These areas can grow in a glandular pattern, forming glands, tubules, cysts or papillae with apical and subnuclear cystoplasmic vacuolation of the columnar epithelial lining or they may express hepatic differentiation, resembling normal liver [3, 4, 39, 40]. Taking into account the fact that in postmenopausal women most of these neoplasms coexist with an ovarian epithelial component, extensive sampling is recommended along with an appropriate immunohistochemical panel that should include AFP.

YST are typically positive for AFP, glypican-3, LIN28, and SALL-4, which show high sensitivity, but low specificity for the discussed tumors and they are negative for OCT4, SOX2, D2-40, and CD30 [3, 42-44]. SALL-4 appears to be the most clinically useful stain in distinguishing YST from other epithelial tumors [3, 42-46]. Other helpful markers in the diagnosis of yolk sac tumors are CDX2 (generally positive in tumors arising from the endoderm) and HEpPar1 (expressed in areas of hepatoid differentiation of YSTs, but in hepatocellular and ovarian hepatoid carcinomas as well) [3, 42]. Furthermore, CK7 and EMA are useful markers for distinguishing YST from carcinomas, as they are not expressed or are expressed weakly in pure YST [44, 47, 48].

Positivity for AFP, glypican-3, CDX2, and SALL-4 and negativity for ER, PR, and PAX-8 favour the diagnosis of glandular/endometrioid-like YST over endometrioid carcinoma [3, 42, 48]. Clear cell carcinoma expresses HNF-1β, EMA, and napsin A and is negative for AFP and SALL-4, in contrast to the glandular, hepatoid, papillary, and reticular patterns of YST with which it may be confused. Both tumors are positive for glypican-3 [3, 22, 44, 47, 48]. Finally, the markers that could distinguish a serous carcinoma compo-

Table1. — *Demographics, diagnosis, treatment and outcome of 46 postmenopausal patients with ovarian yolk sac tumors*

Author (Ref)	Year of publication	No. Of cases	Age at diagnosis (years)	Stage	Histology	Endometriosis	Treatment	Chemotherapy	Outcome
Ashihara *et al*. (35)	2012	1	60	IC	Pure: YST	No	TAH, BSO and retroperitoneal lymphadenectomy	BEP × 5 followed by VeIP × 5	DOD at 21M
Varia *et al. (11)*	2012	1	69	N/A	Mixed: HGSC + YST	No	TAH, BSO and omentectomy	N/A	N/A
Chen *et al. (36)*	2014	1	61	IC	Mixed: YST +HGSC + CCAC	No	TAH, BSO, omentectomy, appendectomy, pelvic and para-aortic lymphadenectomy	TCa × 6	DF at 6M
Yu *et al. (37)*	2014	1	55	IA	Mixed GST + CCAC	No	TAH, BSO, omertectomy, r. infundibulopelvic ligament resection and bilateral paracolic sulci peritoneum Bx	BEP × 7	DF at time of publication
McCarthy *et al*. (3)	2016	1	62	IC3	Mixed:YST + HGSC	No	TAH, BSO, pelvic washings, omental Bx	Adjuvant chemotherapy	DF at time of publication
Wang *et al. (38)*	2016	5	N/A abstract	IC	N/A	N/A	Surgery	4 patients BEP postoperatively	4 patients DOD at 30.8, 18.5, 14.5 and 8.5M after diagnosis
				IIC				1 patient Cisplatin postoperatively	1 patient DF at 40M
				IIC					
				IIB					
				Unclear					
McNamee *et al. (39)*	2016	13	69	IIIC	Mixed: HGSC + YST	No	N/A	N/A	N/A
			59	IIB	Mixed: YST + neuroendocrine	No	N/A	N/A	DOD at 27 M after diagnosis
			64	IIIA	Mixed: HGSC + YST	No	N/A	N/A	N/A
			79	IA	Mixed: YST + borderline CC adenofibroma	No	N/A	N/A	DF at 21 M from diagnosis
			63	IA	Pure: YST	No	N/A	N/A	N/A
			60	IC	Pure: YST	No	N/A	N/A	N/A
			72	IC	Mixed: YST + immature teratoma + carcinoid + EM	No	N/A	N/A	N/A
			56	IIIC	Mixed: YST + HGSC	No	N/A	N/A	DOD at 4M after diagnosis
			73	IC	Pure: YST	No	N/A	N/A	N/A
			62	IIIC	Mixed: HGSC + YST	No	N/A	N/A	DOD at 20M after diagnosis
			73	IA	Pure: YST	No	N/A	N/A	N/A
			68	IIIC	Mixed: HGSC + YST	No	N/A	N/A	DF at 1M after diagnosis
			63	IVB	Mixed: EM + YST	No	N/A	N/A	DOD at 10M after diagnosis

GCT: germ cell tumor, YST: Yolk sac tumor, EM: endometrioid carcinoma, HGSC: high-grade serous carcinoma, CCAC: clear cell adenocarcinoma, TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, Bx: biopsy, Ve: vinblastine, P: cisplatin, Ca:carboplatin, B: bleomycin, E: etoposide, T: taxane, I:ifosfamide, DOD: died from disease, M: months, D: days, DF: disease-free, N/A: not available.

nent from YST are CK7, ER, PR, PAX-8, and WT-1 [3, 49, 50].

According to Nogales *et al.* [42] an antibody panel including markers of pluripotentiality (SALL4 and LIN28) and endodermal identity (AFP, GPC3, and villin) is appropriate for recognizing the multiple differentiations, as well as for identifying unusual histological variants of YST, supporting the recently proposed term of primitive endodermal tumors [22, 39]. One should be aware that some glandular somatic patterns of YST may be negative for AFP or GPC3 and positive for HepPar-1 and CDX2 as already mentioned. However, negativity for AFP or GPC3 in the presence of markers such as villin, LIN28, or SALL4 should not preclude the diagnosis of YST [42].

As already mentioned, pure or mixed ovarian YST in postmenopausal women are rare. Thus, there are limited data regarding the course of the disease, the prognostic factors, and the response to therapy [4-6, 45, 51]. According to the literature, the introduction of bleomycin/ etoposide/ cisplatin (BEP) chemotherapy for malignant germ cell tumors has improved outcomes in premenopausal women, but it does not have a similar impact on postmenopausal patients [4-6, 51]. The mixed tumors usually occurring in the latter age group represent an aggressive variant of ovarian malignancy associated with rapid growth and high stage disease at diagnosis, with the majority of these cases resulting in death secondary to the disease [4, 5, 45 52]. Of the documented cases of pure YST in postmenopausal women, final outcomes have not yet been consistently reported [5].

Conclusion

The authors presented a case of ovarian YST in a postmenopausal woman, adding one more case to the 59 already reported. In the present case, a serous carcinoma along with an endometriotic cyst component existed.

The outcome for postmenopausal patients remains poor, even for those presenting with early stage disease or with pure YST. Further research is required to determine the pathogenesis and plan an effective therapy for this age group.

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