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CASE REPORT

Ovarian yolk sac tumor in a postmenopausal woman: case report and review of the literature

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Abstract Ovarian yolk sac tumor (YST) is a malignant germ cell tumor generally arising in young females and occurs very rarely after menopause. We describe a case of ovarian YST in a 60-year-old postmenopausal woman. The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymphadenectomy for a right ovarian tumor 10 cm in diameter. Microscopic examination revealed that the tumor had the polyvesicular vitelline pattern and the glandular pattern of YST. There were no other types of germ cell tumor or any components of surface epithelial tumors, excluding "heterodifferentiation" of these. Immunohistochemically, tumor cells were positive for α-fetoprotein (AFP), SALL4, and only occasionally positive for cytokeratin 7, and negative for CD15 (leu-M1), and hepatocyte nuclear factor-1 beta. After surgery, the patient received 10 cycles of cisplatin-based chemotherapy. Preoperatively elevated serum AFP decreased to within the normal range after chemotherapy; however, the disease recurred and progressed rapidly, and she died of the disease 21 months after the operation. This case implies that the histogenesis of postmenopausal YST is quite different from that of a germ cell neoplasm in young females and this different histogenesis may cause the resistance to chemotherapy and poor prognosis.

Keywords Yolk sac tumor · Ovary · Postmenopausal woman · Epithelial tumor

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Introduction

Yolk sac tumor (YST) is a type of malignant germ cell tumor with various yolk sac and vitelline structures and is the second most common type of ovarian germ cell tumor, following dysgerminoma. Ovarian YST is generally found in young females and occurs very rarely after menopause [1]. Only a handful of cases of ovarian YST in postmenopausal women have been reported so far and most were associated with benign or malignant epithelial tumors [2–12]. Herein we present a case of YST in a postmenopausal woman that was not accompanied by any epithelial tumors. This case report aims to show the clinical and pathological features of this rare case and includes a current literature review.

Case report

A pelvic mass was incidentally identified on gynecological examination in July 2008 of a 60-year-old, gravida 1, para 1, postmenopausal Japanese woman without any abdominal symptoms. Ultrasonography revealed a pelvic mass about 9 cm in diameter arising in the right ovary. Magnetic

resonance (MR) imaging revealed a predominantly solid tumor about 9.5 × 7 cm in size with striking contrast enhancement. An area of hemorrhage was also found within the tumor (Fig. 1). No metastasis was detected on computed tomography (CT). Preoperative serum tumor marker levels were as follows: α-fetoprotein (AFP), 175,300 ng/ml (normal less than 20 ng/ml); CA-125, 110 U/ml (normal less than 35 U/ml); CA 19-9, 295.4 U/ml (normal less than 37 U/ml). In August 2008, the patient underwent laparotomy with malignant right ovarian tumor as the preoperative diagnosis. At laparotomy, the right ovarian tumor was about 10 cm in diameter and exhibited strong adhesions to the uterus and rectum in the pelvis. She had a very small amount of ascites, which was negative for malignancy on cytology. No macroscopic disseminated lesions of cancer cells were found in either the peritoneum or the greater omentum. Surgical procedures were performed, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymphadenectomy. The surgical stage was stage Ic(b).

Following surgery, cisplatin-based adjuvant chemotherapy consisting of cisplatin, etoposide, and bleomycin (BEP therapy) was started. The patient received three courses of this chemotherapy. Serum concentrations of AFP, CA-125, and CA 19-9 significantly decreased after surgery and chemotherapy. In particular, her serum AFP level, which was extremely high before surgery, rapidly decreased to within the normal range after three courses of BEP therapy (Fig. 2); however, she developed depression at the end of the third course of BEP therapy, making it

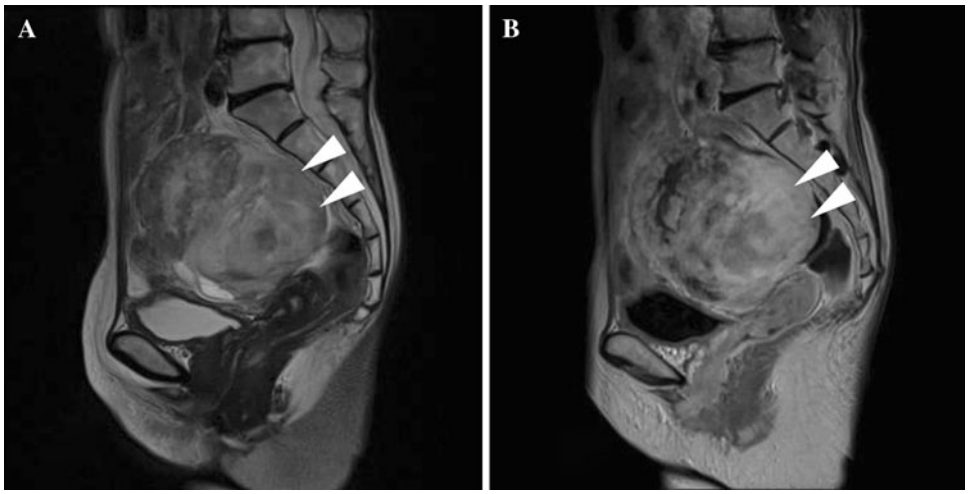

Fig. 1 MR imaging of right ovarian tumor. **a** Sagittal T2-weighted MR image shows a mass (*arrowhead*) that is heterogeneously high in intensity. **b** Sagittal post-contrast MR image shows striking enhancement of the mass (*arrowhead*)

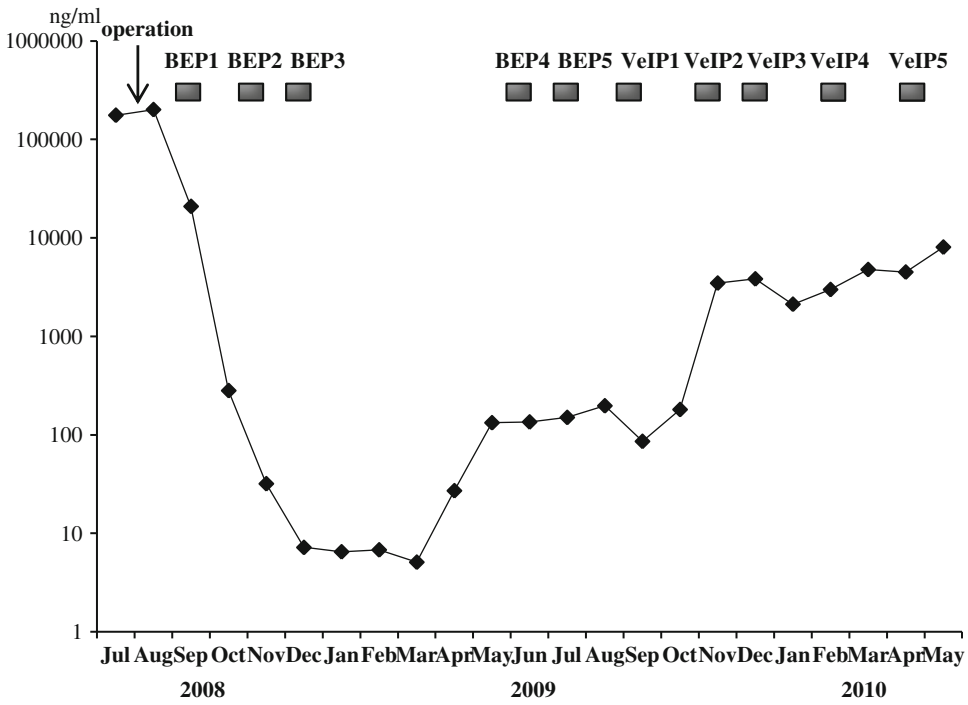

Fig. 2 Changes in serum AFP level

impossible to continue. Four months later, her serum AFP level elevated again, and BEP therapy was resumed; however, her serum AFP level did not decline in spite of two more courses of BEP therapy as salvage chemotherapy: VeIP therapy consisting of vinblastine, ifosfamide, and cisplatin was started. Despite five courses of VeIP therapy, the disease progressed rapidly and she died of the disease 21 months after the operation.

Gross findings

The right ovarian tumor removed from the patient was 12 × 9 × 7 cm, weighed 414 g, and was an elastic and predominantly solid tumor. The surface of the tumor was yellowish and smooth (Fig. 3). The left ovary, fallopian tubes, and uterus were unremarkable.

Microscopic findings

In the right ovarian tumor, atypical cells proliferated and exhibited various shapes; however, the tumor could be roughly divided into two components (Fig. 4): one consisted of many vesicles lined with flattened cells and surrounded by connective stromal tissue. Individual vesicles also varied in shape, and some had an hourglass shape. This component appeared to represent the polyvesicular vitelline pattern of YST. The other consisted of columnar or cuboidal cells that formed primitive glandular structures and were surrounded by loose, edematous, or hyalinized connective tissue. This component appeared to represent the glandular pattern of YST. Thus, this ovarian tumor showed characteristics consistent with ovarian YST. There were no other types of germ cell tumor or any elements consistent with ovarian epithelial malignant or benign neoplasm.

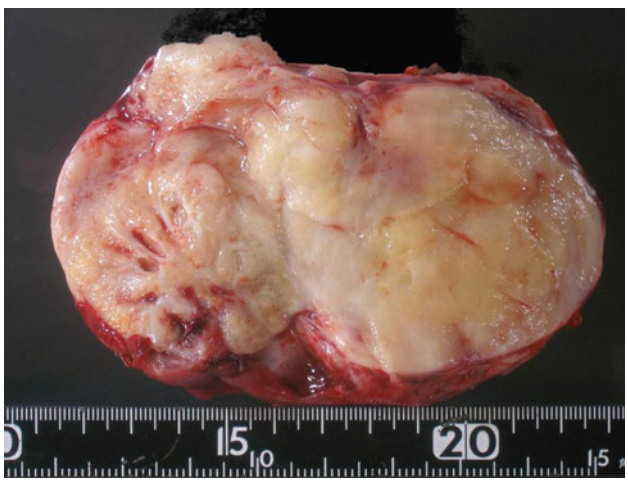

Fig. 3 Resected specimen composed of right ovarian tumor. Gross appearance of right ovarian tumor showed an elastic and predominantly solid tumor with smooth surface

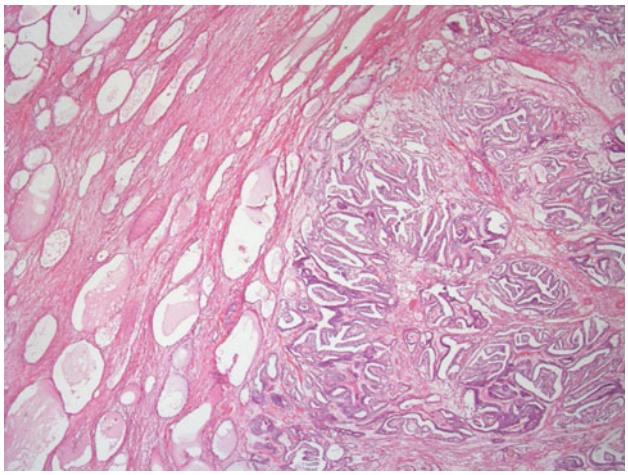

Fig. 4 YST with polyvesicular vitelline pattern on the left and glandular pattern on the right (H&E staining)

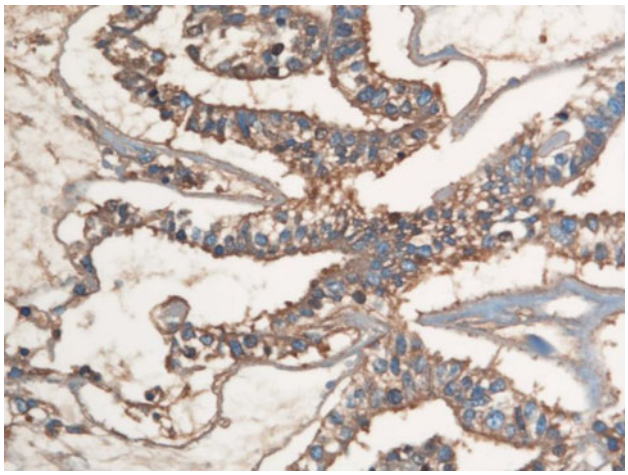

Fig. 5 YST with positive immunohistochemical staining for α-fetoprotein (AFP)

Immunohistochemical findings

Immunohistochemically, neoplastic cells were positive for AFP (polyclonal, 1:500; Dako, Glostrup, Denmark) (Fig. 5), SALL4 (clone; 6E3, 1:500, Abnova, Taipei, Taiwan) (Fig. 6), and negative for CD15 (clone; BY87, 1:50; Novocastra, Newcastle, UK) and hepatocyte nuclear factor-1 beta (HNF-1 beta, clone; C20, 1:200; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Only occasional cells were positive for cytokeratin 7 (CK 7, clone; OV-TL 12/30, 1:100; Dako) (Fig. 7).

Discussion

Although ovarian YSTs rarely occur after menopause, in the case under discussion, preoperative CT/MR images

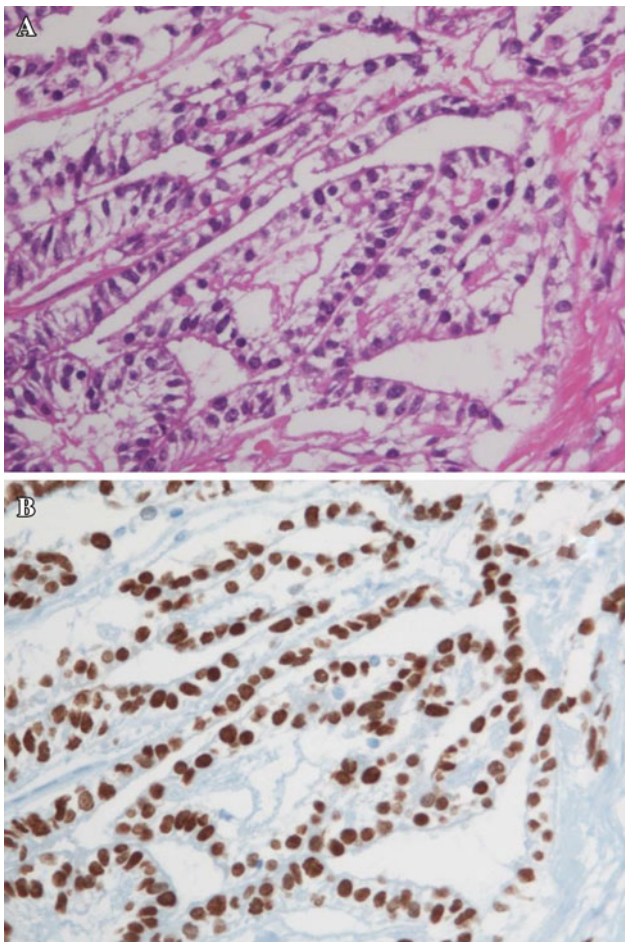

Fig. 6 YST with H&E staining (**a**) and immunohistochemical staining for SALL4 (**b**). YST is positive for SALL4 (**b**)

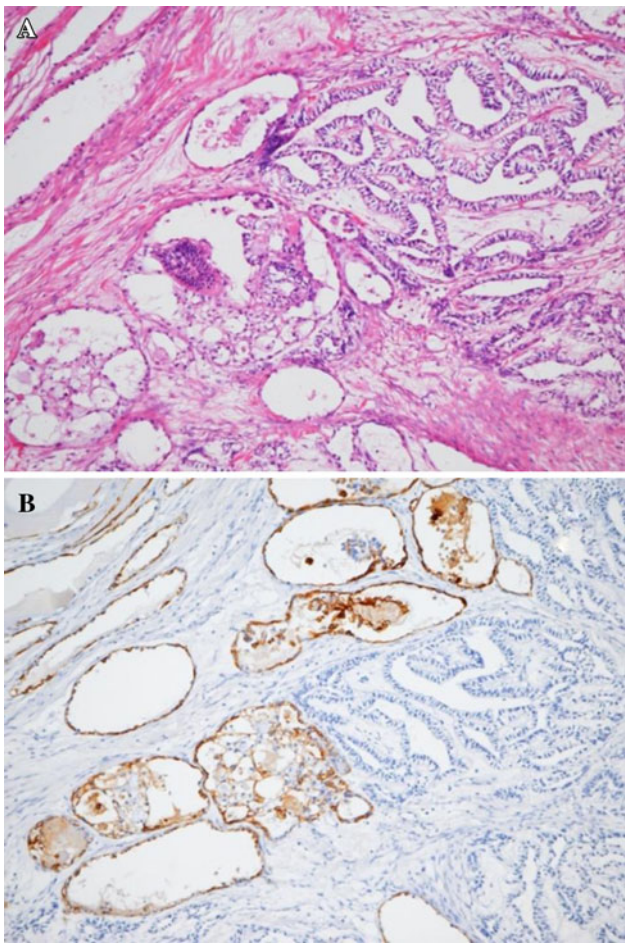

Fig. 7 YST with H&E staining (**a**) and immunohistochemical staining for cytokeratin 7 (CK 7) (**b**). The glandular pattern, on the *right*, is negative for CK 7 (**b**). The polyvesicular vitelline pattern, on the *left*, is positive for CK 7 (**b**)

demonstrated features characteristic of YST, such as a large predominant solid mass with some cystic changes and areas of hemorrhage [13]. Histologically, YST shows a variety of architectures, including microcystic or reticular, endodermal sinus, solid, alveolar-glandular, polyvesicular vitelline, myxomatous, papillary, macrocystic, hepatoid, and glandular patterns [1]. Although different patterns may coexist in the tumor, one or two patterns are usually predominant [1]. The polyvesicular vitelline and glandular patterns as observed in this particular case are characteristic of ovarian YST.

The diagnosis of ovarian YST is sometimes difficult because some morphological patterns of YST resemble malignant surface epithelial tumors. For example, the glandular pattern of YST may impart a close resemblance to endometrioid adenocarcinoma (EAC) [4] and glandular, papillary, and hepatoid patterns of YST can be incorrectly regarded as clear cell carcinoma (CCC) [14]. More importantly, in postmenopausal age tumors with features of YST have been reported to be associated with surface epithelial tumors, possibly as a consequence of "hetero-differentiation" [2–6, 14]. Therefore, in the current case, a serious diagnostic concern was CCC, necessitating extensive sampling of the tumor and immunohistochemical study. Elevated serum AFP concentration and positive immunostaining for AFP are certainly typical of YST [1], but these findings have also been reported in several ovarian carcinomas of somatic origin [15–17]. Ramalingam et al. [18] reported that CK 7 is a useful marker to distinguish YST from EAC and CCC, because CK 7 is negative in YST but is diffusely positive in both EAC and CCC. Negative staining for CK 7 in cells with a glandular pattern in this tumor indicated that this case was YST without EAC and CCC. Although Ramalingam et al. [18] also reported that polyvesicular and reticular patterns of YST were negative for CK 7, staining for CK 7 was positive in cells with a polyvesicular vitelline pattern in this case. The reason for the discrepant staining is undefined. Nevertheless, Devouassoux-Shisheboran et al. [19] showed that the hepatoid pattern of YST was negative, but

Table 1 Previously reported YST in postmenopausal women

References	Patient age (years)	Laterality	Preoperative serum AFP (ng/ml)	Histology	Staging	Primary surgery	Chemotherapy (cisplatin based)	Outcome (after surgery)
Brown and Green [10]	57	L	NA	Pure YST	NA	NA	None	Dead, 3 months
Ferracini et al. [7]	63	NA	NA	YST	NA	Exploratory laparotomy	None	Dead, 2 days
Mazur et al. [11]	82	R	NA	Mucinous cystadenofibroma-YST	NA	TAH–BSO Partial omentectomy Para-aortic LN biopsy, liver biopsy	NA	Alive, 24 months
Kinoshita [8]	62	R	10,408	Pure YST	Ia	TAH–BSO	7 cycles	Alive, NA
Nogales et al. [4]	64	L	>300	EAC-YST	Ia	TAH–BSO	3 cycles	Dead, 14 months
	71	R	Negative	EAC-YST	Ia	TAH–BSO	6 cycles	Alive, 12 months
	71	R	NA	EAC-YST	III	TAH–BSO	1 cycle	Dead, 3 months
	73	L	23	Carcinosarcoma-YST	III	LSO Ometntectomy Appendix and uterine biopsies	Cisplatin based NA	Alive 2 months
Horiuchi et al. [2]	53	L	2,842	EAC-YST	Ia	TAH–BSO Omentectomy Pelvic lymphadenectomy	6 cycles	Dead, 6 months
Arai et al. [6]	71	R	56	Mucinous cystadenocarcinoma-YST	Ic	TAH–BSO	Cisplatin based NA	Dead, 6 months
Oh et al. [9]	75	R	17,318	Pure YST	IIIc	TAH–BSO Omentectomy Sigmoid colectomy, pelvic node biopsy	3 cycles	Dead, 4 months
Kamoi et al. [3]	54	R	13,140	EAC-YST	Ic	TAH–BSO Partial omentectomy Appendectomy	5 cycles	Alive, 21 months
Lopez et al. [5]	51	R	37	EAC-YST, mucinous cystadenoma	Ic	TAH–BSO Omentectomy	4 cycles	Dead, 10 months
Abe et al. [12]	52	L	24,518	EAC-YST	Ic	TAH–BSO Pelvic lymphadenectomy Para-aortic lymphadenectomy	6 cycles	Alive, 20 months
Present study	60	R	200,000	Pure YST	Ic	TAH–BSO Pelvic lymphadenectomy	8 cycles	Dead, 22 months

YST yolk sac tumor, *EAC* endometrioid adenocarcinoma, *TAH–BSO* total abdominal hysterectomy and bilateral salpingo-oophorectomy, *LN* lymph node, *NA* not available, *L* left, *R* right

polyvesicular and reticular patterns were positive for CK 7, as in our case. Thus, CK 7 staining of polyvesicular and reticular patterns of YST remains controversial. In addition, tumor cells in this case were negative for CD15. CD15 was also reported to be useful marker to distinguish YST from CCC because it was expressed strongly in CCC but was weakly or not expressed in YST [18]. Finally, SALL4, a novel diagnostic marker for germ cell tumor, was positive, and HNF-1 beta, expressed by CCC, was negative in our case [20, 21]. These results and the absence of convincing features of CCC established the diagnosis of postmenopausal pure ovarian YST.

All 15 reported cases of YST in postmenopausal women are shown in Table 1 [2–12]. The average age at onset was 63.9 years. The laterality of all tumors was unilateral, as in YST in young females [22]. Positive serum AFP was found in all patients with a YST component in young females at diagnosis [22]. Elevated preoperative serum AFP was also observed in all seven available cases of postmenopausal ovarian YST, although it was low in one case. In all cases, laparotomy was performed as the primary therapy, as for YST in young females. The number of surgical stage I, II, III, and IV was 9, 0, 3 and 0 cases, respectively, and the stage was not available in three cases. In other words, 75% of postmenopausal ovarian YSTs were found in stage I. Approximately 60–70% of ovarian YSTs in young females are stage I or II, and the stage distribution at diagnosis is quite different from that of epithelial ovarian cancer usually found in advanced stage [22, 23]. From this point of view, postmenopausal ovarian YST does not resemble epithelial ovarian cancer, but YST in young females.

The prognosis of YST in this patient was different from typical YST in young females but similar to previously reported YST in older females. YST of the ovary in young females is sensitive to cisplatin-based chemotherapy [22]. Cisplatin-based chemotherapy, such as BEP therapy, has improved the prognosis of YST. Nawa et al. [24] reported that the 5-year survival rate of YST in young females was 92.5, 75, 30, and 25% for patients with stage I, II, III, and IV, respectively. Postoperative adjuvant cisplatin-based chemotherapy has been performed for all postmenopausal YST since 1990; however, the prognosis of YST in postmenopausal women is very poor even in stage I cases and most patients died of the tumor depending on the stage. The survival rate in stage I was 62.5% (5/8) at 1 year and 0% (0/5) at 2 years; two more patients died within 2 years postoperatively. Two patients in stage III died of the disease within 4 months after operation. BEP and VeIP therapy was resumed since the serum AFP level increased again in this patient, because cisplatin-based second-line chemotherapy has proven to be curative in many women with refractory ovarian germ cell tumor, including those who had been heavily pretreated, unlike epithelial ovarian carcinoma [25]; however, the serum level of AFP did not decline before her death. Considering these previously reported cases and our present case, the chemosensitivity of postmenopausal YST seems poor and quite different from that of typical YST as most authors have reported that YST in postmenopausal women is resistant to cisplatin-based chemotherapy [2, 4–6, 9].

Only three cases of pure YST after menopause have been reported so far and this tumor is the fourth case [8–10]. Most recent cases of postmenopausal YST were associated with epithelial tumor. There is no significant difference between pure YST and YST with epithelial tumor in age at onset, laterality of the tumor, serum AFP positive rate, stage distribution, and prognosis, but a slight difference in the histogenesis, as mentioned below.

YST is generally a malignant germ cell neoplasm that is thought to originate from undifferentiated and multipotential embryonal carcinoma by selective differentiation toward yolk sac or vitelline structures [1]. Nevertheless, the histogenesis of postmenopausal YST is unclear. It has been reported that elevated serum AFP concentration was observed in several ovarian carcinomas of somatic origin [15–17]. These findings indicate that somatic carcinoma has the ability to differentiate into germ cells. Consequently, some authors have suggested that the yolk sac component is derived from somatic mesodermal carcinoma through a neometaplastic process in postmenopausal YST with epithelial carcinoma [2–5, 12]. On the other hand, postmenopausal pure YST does not have somatic mesodermal carcinoma that differentiates into YST and is proposed to originate from ovarian surface epithelium through a neometaplastic process [1, 9]. Anyway postmenopausal YST is thought to be derived from epithelial cells not germ cells. In other words, the histogenesis of postmenopausal YST with or without epithelial carcinoma is quite different from that of a germ cell neoplasm in young females [1, 9]. This different histogenesis may cause the resistance to cisplatin-based chemotherapy and poor prognosis of postmenopausal YST in spite of diagnosis at an early stage; therefore, specific chemotherapy depending on the histogenesis will be necessary after further investigations.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Talerman A (2002) Germ cell tumor of the ovary. In: Kurman RJ (ed) Blaustein's pathology of the female genital tract, 5th edn. Springer, New Yolk, pp 978–988
2. Horiuchi A, Osada R, Nakayama K et al (1998) Ovarian yolk sac tumor with endometrioid carcinoma arising from endometriosis in a postmenopausal woman, with specific reference to expression of α-fetoprotein, sex steroid receptors, and p53. Gynecol Oncol 70:295–299

3. Kamoi S, Ohaki Y, Okada S et al (2002) A case of ovarian endometrioid adenocarcinoma with yolk sac tumor component in a postmenopausal woman. APMIS 110:508–514
4. Nogales FF, Bergeron C, Carvia RE et al (1996) Ovarian endometrioid tumor with yolk sac tumor component, an unusual form of ovarian neoplasm. Am J Surg Pathol 20:1056–1066
5. Lopez JM, Malpica A, Deavers MT et al (2003) Ovarian yolk sac tumor associated with endometrioid carcinoma and mucinous cystadenoma of the ovary. Ann Diagn Pathol 7:300–305
6. Arai T, Kitayama Y, Koda K (1999) Ovarian mucinous cystadenocarcinoma with yolk sac tumor in a 71 year old woman. Int J Gynecol Pathol 18:277–280
7. Ferracini R, Gardini G, Lanzanova G et al (1979) Endodermal sinus tumor in a 63 year old female. Pathologica 71:885–887
8. Kinoshita K (1990) A 62-year-old woman with endodermal sinus tumor of the ovary. Am J Obstet Gynecol 162:760–762
9. Oh C, Kendler A, Hernandez E (2001) Ovarian endodermal sinus tumor in a postmenopausal woman. Gynecol Oncol 82:392–394
10. Brown JR, Green JD (1976) Yolk sac carcinoma. South Med J 69:728–731
11. Mazur MT, Talbot WH Jr, Talerman A (1988) Endodermal sinus tumor and mucinous cystadenofibroma of the ovary: occurrence in an 82-year-old woman. Cancer 62:2011–2015
12. Abe A, Furumoto H, Yoshida K et al (2008) A case of ovarian endometrioid adenocarcinoma with a yolk sac tumor component. Int J Gynecol Cancer 18:168–172
13. Yamaoka T, Togashi K, Koyama T et al (2000) Yolk sac tumor of the ovary: radiologic–pathologic correlation in four cases. J Comput Assist Tomogr 24:605–609
14. Ballota MR, Bianchini E, Borghi L et al (1995) Clear cell carcinoma simulating the "endometrioid-like variant" of yolk sac tumor. Pathologica 87:87–90
15. Bose CK, Mukherjea M (1993) Alpha-fetoprotein in advanced epithelial cancer. Br J Obstet Gynecol 100:1149–1150
16. Higuchi Y, Kouno T, Teshima H et al (1984) Serous papillary cystadenocarcinoma with α-fetoprotein production. Arch Pathol Lab Med 108:710–712
17. Konishi I, Fujii S, Kataoka N et al (1988) Ovarian mucinous cystadenocarcinoma producing α-fetoprotein. Int J Gynecol Pathol 7:182–189
18. Ramalingam P, Malpica A, Silva EG et al (2004) The use of cytokeratin 7 and EMA in differentiating ovarian yolk sac tumors from endometrioid and clear cell carcinomas. Am J Surg Pathol 28:1499–1505
19. Devouassoux-Shisheboran M, Schammel DP, Tavassoli FA (1999) Ovarian hepatoid yolk sac tumours: morphological, immunohistochemical and ultrastructural features. Histopathology 34:462–469
20. Cao D, Guo S, Allan RW et al (2009) SALL4 is a novel sensitive and specific marker of ovarian primitive germ cell tumors and is particularly useful in distinguishing yolk sac tumor from clear cell carcinoma. Am J Surg Pathol 33:894–904
21. Tsuchiya A, Sakamoto M, Yasuda J et al (2003) Expression profiling in ovarian clear cell carcinoma: identification of hepatocyte nuclear factor-1 beta as a molecular marker and a possible molecular target for therapy of ovarian clear cell carcinoma. Am J Pathol 163:2503–2512
22. Dällenbach P, Bonnefoi H, Pelte MF et al (2006) Yolk sac tumours of the ovary: an update. Eur J Surg Oncol 32:1063–1075
23. Heintz AP, Odicino F, Maisonneuve P et al (2001) Carcinoma of the ovary. J Epidemiol Biostat 6:107–138
24. Nawa A, Obata N, Kikkawa F et al (2001) Prognostic factors of patients with yolk sac tumors of the ovary. Am J Obstet Gynecol 184:1182–1188
25. Tewari K, Cappuccini F, Disaia PJ et al (2000) Malignant germ cell tumors of the ovary. Obstet Gynecol 95:128–133