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Case Report

Vulvar yolk sac tumor diagnosed during pregnancy, with recurrence during subsequent second pregnancy

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Introduction

Endodermal sinus tumor or yolk sac tumor (YST) is an uncommon germ cell malignancy. In a 30-year population-based study of female malignant germ cell tumors using the SEER database, only 14.5% (183 of 1262) of cases were YST (Smith et al., 2006). 90% of female germ-cell tumors occur in the ovaries, with only 10% arising in extra-gonadal sites such as the sacro-coccygeal region, peritoneum, mediastinum, central nervous system, pineal gland, liver and genital tract (Pasternack et al., 2008). The various extra-gonadal locations of YST are explained by embryonic migration of primordial germ cells from their origin in the caudal portion of the yolk sac, to their incorporation into primitive sex cords (Pasternack et al., 2008). The primordial germ-cells may be either arrested or misplaced at various points along the migration route.

The majority of extra-gonadal YST in the female genital tract occur in the vagina or cervix (Flanagan et al., 1997). YST of the external genitalia is exceptionally rare, with only 15 cases of primary vulvar YST reported in published literature between 1978–2014 (Table 1). The origin of primary vulva YST is believed to be misplaced germ-cells during embryonic life entering the vulva through the gubernaculum (Flanagan et al., 1997). Reported cases of primary vulvar YST ranged in age from 22 months to 52 years, with most cases reported in the 2nd and 3rd decade of life (Subrahmanya et al., 2011), at a female's reproductive peak. Only one vulvar YST has previously been reported in pregnancy (Krishnamurthy and Sampat, 1981). We present the second case of a vulvar YST occurring in a pregnant patient, with the first reported incidence of tumor recurrence during a subsequent pregnancy.

Case report

A 27-year-old Indonesian-born female presented 27 weeks into her first pregnancy with a 3 week history of a rapidly enlarging right vulvar mass. She had no significant prior medical or family history.

On examination, a 5 cm firm, mobile mass was palpable in the right labia majora, with no regional lymphadenopathy (Fig. 1A). Fine needle aspiration of the lesion revealed a poorly differentiated malignancy. Pelvic magnetic resonance imaging (MRI) showed a well-defined 51×34×29mm mass in the right labia majora; with no evidence of adjacent urethral or vaginal invasion; and no pelvic or inguinal nodal involvement. At 29 weeks gestation, the patient underwent a radical wide local excision of the right vulvar area. The incompletely excised, encapsulated, subcutaneous lesion measured 80×40×40mm (Fig. 1B). The lesion consisted of extensive areas of microcystic/reticular growth pattern, with occasional Schiller-Duval bodies (Fig. 2A) typical of YST, confirmed by positive immunohistochemistry staining for both glypican-3 (Fig. 2B) and alpha-feto protein (AFP). Lymphovascular invasion was not identified. The patient's AFP dropped from 192 μg/L pre-operatively, to 56 μg/L post-operatively.

An elective Caesarean section was performed at 32/40 weeks, with a resulting healthy female infant. Intra-operatively, macroscopically normal ovaries were identified. The patient received 4 cycles adjuvant chemotherapy with BEP (Bleomycin 30,000 IU Days 1, 8, 15; Etoposide 100 mg/m^2 Days 1–5, Cisplatin 20 mg/m^2 Days 1–5). Post-chemotherapy CT scans showed no metastatic disease and nadir AFP to 1.2 μg/L.

At 8 months follow-up, post adjuvant chemotherapy, the patient reported not having resumed her periods and was not using contraception, despite medical advice to the contrary. 9 months post completion of BEP, the patient became pregnant again. At 21 weeks gestation, the patient complained of vulvar thickening at the previous surgical site. Her AFP was elevated at 146 μg/L but this was difficult to interpret in

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Table 1
Summary of the literature of vulvar YST case reports.

Author	Age (Y)	Location	Surgery	Tumor Size (cm)	Initial adjuvant treatment	Relapse	Site of relapse	Treatment at relapse	Follow-up
Ungerleider et al. (1978)	15	R labium majus	Radical vulvectomy	4 × 1	VAC	Yes @ 12 m	Inguinal LN	Pelvic LND VD pelvic RT	DoD 23 m
Castaldo et al. (1980)	2	Clitoris	WLE	1.2 × 1.5 × 1.0	No	No			DF 42 m
Krishnamurthy and Sampat (1981)	26	L labium majus	Local excision (8 m pregnant)	7 × 6	No	Yes @ 6 m	Primary + Inguinal LN + Pleural effusion	Re-excision recurrent primary + inguinal LND VA	DoD 11 m
Dudley et al. (1983)	2	R labium majus	Radical vulvectomy + LND + removal of R pubic ramus	6	C + pelvic RT	Yes @ 3 m	Bone, epidural space T12/L1	Decompression laminectomy VAC × 4	DoD 6 m
Penkar et al. (1992)	25	R labium majus	WLE	10 × 7	?	?	?	?	?
Craighead and du Toit (1993)	24	L labium majus	WLE	4 × 4	BEP × 3	Yes @ 6 m Again + 2 m	Inguinal LN Inguinal LN	VAC + BEP + M Groin WLE Pelvic RT 40Gy	DF 15 m
Flanagan et al. (1997)	18	R labium majus	Modified radical vulvectomy + LND	4 × 2.5 × 2	BEP × 3	No			DF 18 m
Traen et al. (2004)	19	R labium majus	Hemi-vulvectomy + LND	2 × 3.5	EP × 3	Yes @ 16 m	Primary + lung + pleura	Lung resection + talc pleurodesis TIP × 3 TI × 2 High-dose CE + AutoSCT × 2	DF 56 m
Khunamornpong et al. (2005)	30	R labium majus	Excisional biopsy Biopsy R inguinal node (3 wks later)	3.5 × 3 × 2.8	PVB × 2	Yes @ 2 m	Primary + inguinal scar	BEP × 3 pelvic RT 60Gy	DF 90 m
Basgul et al. (2006)	32	R labium majus	Hemi-vulvectomy + LND	3.5 × 3.5 × 4	No	Yes @ 6 m	Primary + inguinal LN	BEP × 3	DF 40 m
Niwa et al. (2007)	52	R labium majus	Modified radical vulvectomy + LND	3.5 × 3.0 × 3.0	BEP × 6	No			DF 67 m
Kurucu et al. (2011)	3	L labium majus + clitoris	Partial excision	12 × 5 × 2	BEP × 6	Yes @ 10 m	Primary	ICE × 4	DF 28 m
Subrahmanya et al. (2011)	23	R labium majus	Local excision	6 × 5 × 3	No	Yes @ 2 m	Primary + inguinal LN	?	?
Yin-Yi Chang et al. (2011)	14	L labium majus	Partial excision	5 × 4	BEP × 3 Followed by vulvectomy + LND	Yes @ 8 m Again + 12 m	Inguinal LN Lung + mediastinal LN	Pelvic RT 60Gy Lung resection + mediastinal LND TIP × 4 + Auto SCT × 2 GemOx × 3	DF 18 m
Mochizuki et al. (2012)	1	R labium majus	Partial resection	3	PVB × 5	Yes @ 91 m	Primary + bone + lung	Local excision of primary recurrence VIP × 4	DF 100 m
Present Case (2012)	27	R labium majus	WLE	8 × 4 × 4	BEP × 4	Yes @ 17 m	Primary + pelvic LN + mediastinal LN + lung	Local excision of primary recurrence TIP × 2 High dose CE + Auto SCT × 2	DoD 31 m

VAC: vincristine, actinomycin D, cyclophosphamide.
LN: lymph node.
LND: lymph node dissection.
VD: vincristine, doxorubicin.
RT: radiotherapy.
DoD: died of disease.
WLE: wide local excision.
DF: disease free.
VA: vincristine, actinomycin D.
C: cyclophosphamide.
BEP: bleomycin, etoposide, cisplatin.
M: methotrexate.
EP: etoposide, cisplatin.
TIP: paclitaxel, ifosfamide, cisplatin.
TI: paclitaxel, ifosfamide.
CE: carboplatin, etoposide.
Auto SCT: autologous stem cell transplant.
PVB: cisplatin, vincristine, bleomycin.
ICE: ifosfamide, carboplatin, etoposide.
GEMOX: gemcitabine, oxaliplatin.
VIP: vincristine, ifosfamide, cisplatin.

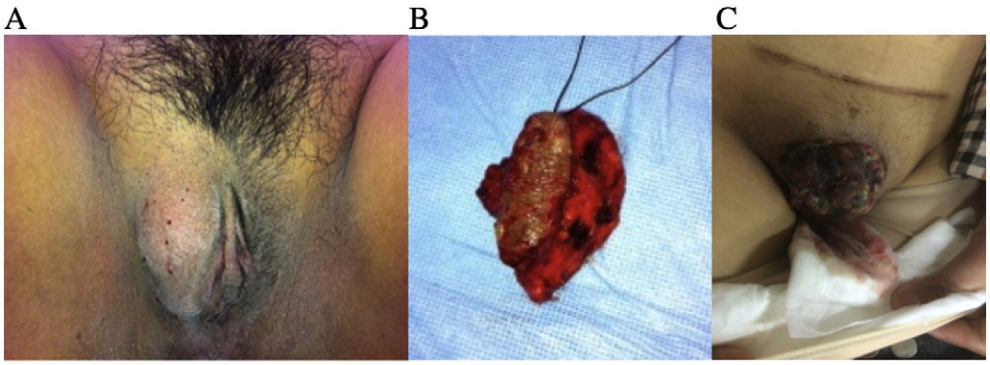

Fig. 1. A: 5 cm firm, mobile mass in the right labia majora on initial presentation; B: Macroscopic appearance of excised lesion 80×40×40mm; C: Exophytic ulcerated recurrent vulvar YST, causing bleeding.

the context of her pregnancy. A subsequent biopsy revealed recurrent YST. MRI pelvis performed at 30/40 weeks showed no evidence of metastatic disease. The right vulvar recurrence was excised at 31/40 weeks. Histopathology confirmed recurrent YST (50×40×40mm), with extensive lymphovascular invasion and close surgical margins (<0.1 mm).

Post discussion at a multi-disciplinary tumor board, the recommendation was again for an elective Caesarean-section at 32/40 weeks, followed by salvage chemotherapy with rescue autologous stem cell transplant (SCT). However the patient declined these recommendations and elected to carry the pregnancy to term, before having a Caesarean section resulting in a second healthy baby girl.

Subsequent examination 1 week post Caesarean section showed a recurrent 2 cm right vulvar nodule, with new right common femoral and external iliac nodal metastases and a solitary pulmonary metastasis in the left upper lobe, identified on CT. The patient went on to have 2 cycles of salvage chemotherapy with TIP (Paclitaxel 175 mg/m^2 Day 1, Ifosfamide 1200 mg/m^2 Days 1–5 with Mesna, Cisplatin 20 mg/m^2 Days 1–5), commencing 2 weeks post-partum. Her AFP fell from 124 μg/L prior to TIP; to 34 μg/L post cycle 1 of TIP, but alarmingly rose back to 133 μg/L post cycle 2 of TIP. Repeat imaging following 2 cycles of TIP revealed a mixed radiological response, with improvement in her pelvic lymphadenopathy, but progression of her primary vulvar tumor, as well as new aorto-pulmonary lymphadenopathy.

At this point, the vulvar mass became increasingly ulcerated and exophytic (Fig. 1C), causing bleeding, and patient required hemostatic radiotherapy (20 Gy/5 fractions). She subsequently underwent stem cell collection with Pegylated Granulocyte colony stimulating factor and Plerixafor, and proceeded onto tandem cycles of high dose chemotherapy with Carboplatin(700 mg/m^2)/Etoposide(850 mg/m^2), with autologous SCT. Post the first transplant, her AFP dropped to 35 μg/L, however at 6 weeks post 2nd transplant, her AFP had risen again to 207 μg/L. A repeat staging CT confirmed disease progression in all sites (primary vulvar, pelvic, mediastinal and lung metastasis) (Fig. 3). The patient died as a result of progressive pleural and pulmonary disease, 31 months after her initial diagnosis, during the first pregnancy. Her 2 babies remain healthy, with normal developmental milestones, at age 12 months and 2 1/2 years respectively.

Discussion

Vulvar YST is a rare and aggressive extra-gonadal germ-cell tumor. In 9 of 15 cases in the reported literature, recurrent or metastatic disease occurred within 12 months of primary surgery, often despite adjuvant chemotherapy. The most common site of recurrence is the inguinal lymph nodes (Subrahmanya et al., 2011; Krishnamurthy and Sampat, 1981; Basgul et al., 2006; Craighead and du Toit, 1993; Khunamornpong et al., 2005; Traen et al., 2004; Ungerleider et al., 1978; Yin-Yi Chang et al., 2011); with lungs being the most common site of distant metastases (Krishnamurthy and Sampat, 1981; Traen et al., 2004; Yin-Yi Chang et al., 2011; Mochizuki et al., 2012).

Extrapolating from evidence-based paradigms in gonadal germ-cell tumors, the optimal management of vulvar YST should involve complete surgical excision, followed by timely adjuvant chemotherapy. Amongst the 10 reported cases of vulvar YST since 1993, 6 cases used BEP as first line systemic therapy, with a median DFS of 28.2 months.

The use of autologous SCT following high dose chemotherapy, as salvage treatment for relapsed gonadal germ cell tumors is well established (Ammakkanavar et al., 2014; Einhorn et al., 2007). However scant literature exists to support the same approach in extra-gonadal germ cell tumors, given disease rarity. We were encouraged by the

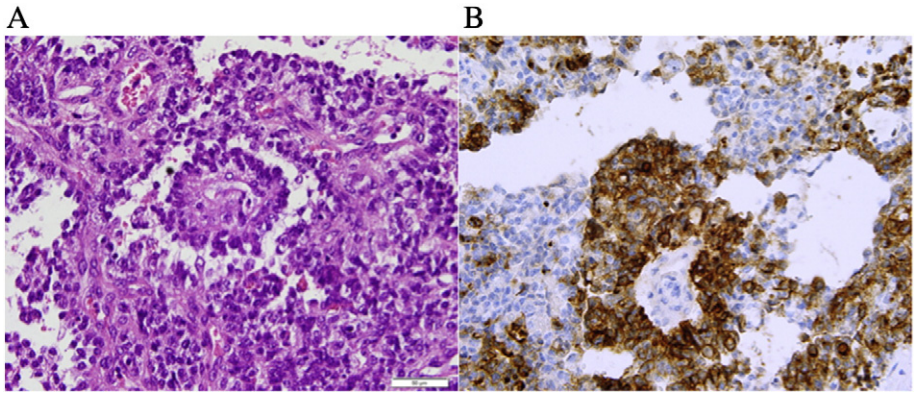

Fig. 2. A: 40× Haematoxylin and Eosin staining, showing Schiller-Duval body; B: Positive immunohistochemistry staining for Glypican 3.

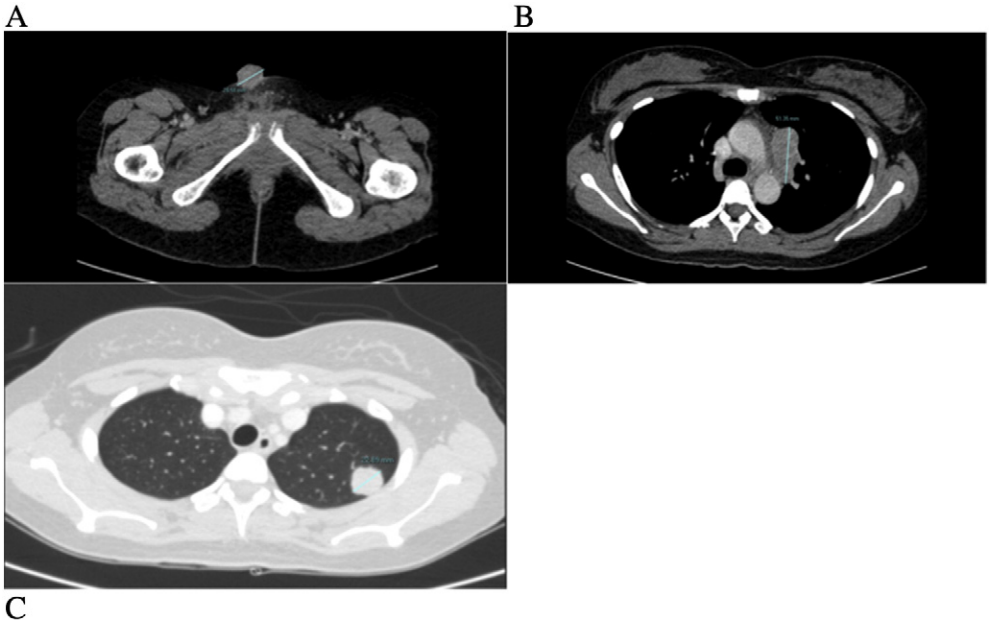

Fig. 3. Post tandem autologous SCT, progressive disease on restaging CT Chest/Abdomen/Pelvis. 3A: vulvar primary; 3B: left mediastinal nodal mass; 3C: left upper lobe – lung.

success of 2 case reports describing long term disease-free-survival in patients with recurrent vulvar YST, post salvage chemotherapy and autologous SCT (Traen et al., 2004; Yin-Yi Chang et al., 2011). Traen et al. (Traen et al., 2004) reported that 16 months after a hemi-vulvectomy and adjuvant Etoposide, Cisplatin (EP), a patient developed lung metastases, which resected. She was subsequently given 2nd-line TIP chemotherapy and autologous SCT and remained disease free at 40 months of follow-up. Yi-Yi Chang et al. (Yin-Yi Chang et al., 2011) reported a 14 year old patient with vulvar YST treated with adjuvant BEP × 3, who developed local recurrence and inguinal nodal disease 8 months later and was subsequently treated with radiation (60 gy/30 fractions). A year post radiation, she developed lung and mediastinal nodal metastasis, and underwent a lung wedge resection and mediastinal nodal dissection. This was followed by 4 cycles of high dose TIP chemotherapy, tandem autologous SCT and 3 cycles of Gemcitabine, Oxaliplatin (GEMOX) chemotherapy. The patient was alive and disease free at 18 months post SCT.

In the only other case of vulvar YST in a pregnant patient (Krishnamurthy and Sampat, 1981), chemotherapy was not administered after the initial excision. Six months later, the disease recurred in the vulva along with enlarged inguinal nodes, requiring an additional excision. The patient was only then placed on adjuvant chemotherapy (VAC); however, she died 4 months later due to lung metastases.

Our patient recurred with YST during her 2nd pregnancy at 28/40 weeks. Recurrences of ovarian germ cell tumors during pregnancy have previously been described in several case reports (Tao et al., 2011; Weed et al., 1979). However, this is the 1st reported case of a vulvar YST, or indeed any extra-gonadal germ cell tumor, which was diagnosed in pregnancy and treated with systemic adjuvant chemotherapy; that recurred during a subsequent pregnancy. The timing of recurrence in our case is curious but one would have to assume coincidental, as there is no biological rationale why the pregnancy milieu would predispose to recurrence. A similar situation in an ovarian YST has been previously described by Weed et al. (Weed et al., 1979) in 1979. This case involved a 16-year-old female who was diagnosed in the 1st trimester, who terminated the pregnancy and went on to receive chemotherapy with VAC. The patient had 12 months of relapse free survival, before being diagnosed with YST recurrence during her the 2nd trimester of her second pregnancy. She delivered a healthy baby at 33/40 weeks, but succumbed to disease relapse 8 days post-partum, despite reinstitution of VAC chemotherapy in utero.

Unfortunately, our patient could not be salvaged by high dose chemotherapy and autologous SCT. It is conjectural whether the outcome may have been any different if the patient had accepted salvage chemotherapy earlier following her diagnosis of recurrence at 32/40 weeks, rather than carrying her pregnancy to term. In conclusion, early multidisciplinary input and more experience is needed in the optimal management of an aggressive malignancy such as vulvar YST, especially in the context of concurrent pregnancy.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of interest

No conflict of interests to declare.

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