# Primary yolk sac tumor (endodermal sinus tumor) of the vulva: case report and review of the literature

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**Summary**

*Introduction:* Endodermal sinus tumor (EST) or primary yolk sac tumor (YST) of the vulva is extremely rare and a highly malignant germ cell tumor. Only nine cases of vulvar YST have been reported to the world literature to date. We present the tenth case of endodermal sinus tumor of the vulva.

*Case:* A 32-year-old white virgin presented with a 3.5 cm right labial mass without any other signs or symptoms. Excisional biopsy showed YST with a predominantly solid pattern. Unilateral hemivulvectomy with bilateral inguinal lymphadenectomy was performed. Six months after surgery there was a recurrence. She was treated with three courses of the BEP regimen (bleomycin, etoposide, cisplatin). The patient refused to take any further treatment including radiotherapy. The serum alpha-fetoprotein (AFP) was not elevated at the initial diagnosis however it was elevated during recurrence. The patient is alive with the disease 42 months after the first appearance of the vulvar mass.

*Key words:* Yolk sac tumor; Endodermal sinus tumor; Vulva.

## Introduction

Endodermal sinus tumor (EST) is a highly malignant extraembryonal germ cell tumor, showing selective growth of yolk sac endoderm [1].

The occurrence of this tumor at an extragonadal site is rare. In the lower female genital tract, extragonadal yolk sac tumor (YST) occurs most frequently in the vagina. Vulvar EST is extremely rare. It was first reported by Ungerleider in 1978 in a 15-year-old. To our knowledge, only nine cases of endodermal sinus tumor of the vulva have been reported to date [1-9].

These vulvar tumors appear to be aggressive, with three of the previously reported cases having died and three of the cases, including ours, developing recurrence within one year of presentation. As vulvar EST of the vulva is very rare, the reported cases were treated by various types of surgery with or without adjuvant therapy. Thus, the choice of appropriate treatment is not clear [7, 8]. An overview of the nine previously reported cases and our case are summarized in Table 1. We report the tenth case of primary of vulvar EST together with our management protocol including local excision for biopsy, unilateral vulvectomy and bilateral inguinal lymph node dissection with a chemotherapy regimen.

## Case report

A 32-year-old, white, virgin female presented to a private clinic with the complaint of a right labial mass of one year's duration. She reported that the mass had grown slowly and became infected during this period. A well-circumscribed mass at the anterior part of the right labium majus was revealed on examination. The mass was reported to be covered with ulcerated infected skin at the center, fixed to the underlying tissue and free from the pubic bone underneath. Pelvic magnetic resonance imaging (MRI) examination revealed a lobulated, partly well demarcated tumoral mass measuring 4 x 6 x 6 cm in the fatty tissue of the right vulvar region. There were some lymph nodes measuring 18 x 20 x 35 mm in the right inguinal region. Wide local excision of the area of vulval swelling was done. The excised mass, measuring 6 x 4 x 4 cm, was well demarcated and enclosed by thin connective tissue. It was 3.5 x 3.5 x 4 cm in size with a 2.5 x 2 x 2 cm ulcerated area in the center. The surface of the excised mass was brownish-grey colored and lobulated with hemorrhagic areas.

Microscopically the tumor was composed of heterogenous morphological patterns. These included areas of myxoid stroma harboring microcystic spaces, solid epithelial sheets and gland-like structures. Among these areas a few Schiller-Duval bodies were noticed (Figure 1). There were various degrees of atypia in the neoplastic cells. The atypia was most prominent in the mostly clear cells of the solid sheets. With these histological features the tumor was diagnosed as a yolk sac tumor and immunopositivity of the neoplastic cells with AFP confirmed the diagnosis (Figure 2). The immunohistochemical profile of the tumor cells showed positive vimentin immunoreactivity, negative chromografin immune reactivity and positive CEA immunoreactivity in about 40% of the neoplastic cells.

After the diagnosis the patient was referred to our university hospital for further management of the disease. General and systemic examinations were normal. Routine investigations were within normal limits and her menstrual history was normal. The patient had no significant past medical or family history. Renal and liver function tests were normal. She was mildly anemic with a hemoglobin level of 10 g/dl. Ultrasonography showed normal ovaries and normal uterine endometrial echoes. To rule out metastasis a pelvic ultrasound, computerized tomography of the abdomen and thorax, and bone scan were carried out and resulted negative. Serum alpha-feto protein (AFP) and βhCG levels were normal. However there were palpable lymph nodes in the right vulvar area at the pelvis.

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Table 1. — *Summary of the clinical information of patients with vulvar yolk sac tumors showing the relation between treatment modalities and follow-up outcome.*

| Case no./Author | Age (years) at diagnosis | Size | Tumor location | Treatment | Follow-up |
|---|---|---|---|---|---|
| 1 - Ungerleider (1978) | 15 | NA | Right labium majus | Radical vulvectomy VAC, VAD, Pelvic RT | DOD at 23 months? |
| 2 - Castaldo (1980) | 2 | 1.5 cm | Clitoris | Wide excision | NED at 5.5 years |
| 3 - Krishnamurthy (1981) | 26 | 7 cm | Left labium majus | Excision, local recurrence, reexcision, VAC | DOD at 11 months |
| 4 - Dudley (1983) | 1.8 | 6 cm | Right labium majus | Radical vulvectomy, VAC, Pelvic RT | DOD at 6 months |
| 5 - Penkar (1992) | 25 | 10 cm | Right labium majus | Excision | NA |
| 6 - Craighead (1993) | 24 | 4 cm | Left labium majus | Wide local excision, BEP, VAC, groin RT | Groin met at 5 months, after RT NED at 15 months NED, 18 months |
| 7 - Flanagan (1997) | 18 | 5 cm | Right labium majus | Modified RV and groin lymphadenectomy, BEP | NED, 18 months |
| 8 - Traen K (2004) | 19 | 2.5 | Right labium majus | Wide excision, modified RV, BEP | Metastasis to pleura and lung Resection of the metastasis, NED 56 months after initial diagnosis |
| 9 - Khunamornpong (2005) | 30 | 3.5 cm | Right labium majus | Excision, PVB, BEP, pelvis and groin RT | Local recurrence at 2 months, NED, 90 months |
| 10 - Present case | 32 | 2.5 cm | Right labium majus | Wide local excision, modified bilateral lymphadenectomy, BEP | Did not accept RT, AVD, 40 months |

NA: data not available; NED: no evidence of disease; AVD: alive with disease; DOD: dead of disease; RV: radical vulvectomy; RT: radiation therapy; BEP: bleomycin, etoposide, cyclophosphamide; VAD: vincristine, adriamycin; VAC: vincristine, actinomycin, cyclophosphamide; PVB: cisplatin,vincristine, bleomycin.

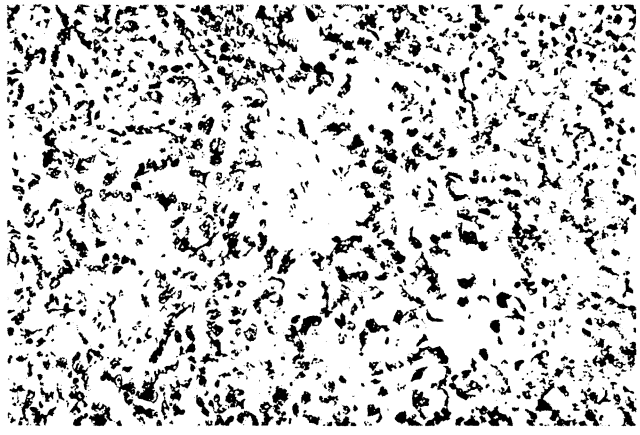

Figure 1. — Schiller duval bodies (H&E x 100).
Figure 2. — AFP immune positivity (DAB x 100).

Bilateral inguinal lymphadenectomy and unilateral vulvectomy were performed. Postoperative recovery was uneventful. Suture removal was done on the ninth day. Pathological results of the material showed that two of the four dissected lymph nodes were tumor-positive on the right side. However, none of the nine lymph nodes dissected on the left side showed infiltration. Management of the case was decided together with the medical oncology team of the university. A BEP (bleomycin, etoposide and cisplatinum) chemotherapy protocol was recommended but the patient refused due to the risk of infertility from the therapy. Follow-up with tumor markers and pelvic MRI were recommended. Six months after surgery, a 1.5 cm nodule developed on the left side of the mons pubis. Pelvic MRI showed multiple conglomerous lymphadenopathies measuring 5 x 3.5 cm in the left inguinal and right obturator regions suggesting metastasis. Serum AFPs showed elevated levels of 23 IU/ml (0.5-5.5). The mass on the mons pubis was excised and histologically confirmed as fat necrosis. Cisplatin-based chemotherapy using cisplatin 60 mg/m$^2$, etoposide 100 mg/m$^2$, and bleomycin 12 mg/m$^2$ (PEB regimen) was administered for three cycles. Adjuvant radiation therapy was also planned. However the patient become depressed because of the disease and refused any further treatment due to infertility risk.

The patient is currently 20 months post chemotherapy and remains alive with the disease 42 months since the first appearance of the mass.

## Discussion

This highly malignant germ cell tumor usually arises in the gonads. However, although extremely rare, tumors of the vulva have been well documented [10].

It has been hypothesized that vulvar germ cell tumors represent misplaced cells that have traveled along the gubernaculum and come to rest in the endodermal sinus of subcutaneous tissues of the mons and labia during embryogenesis [11].

The tumor invades locally and spreads through the lymphatics [10]. Histologically cells are with prominent nucleoli and pink cytoplasm staining positively for AFP. Recurrence and metastasis following simple or extended surgical excision is almost inevitable [1, 2]. The macroscopic findings of EST were available in six cases in the literature (and ours) which showed well-circumscribed masses [3, 5-9]. The reported location of the masses was the right labium in seven cases, the left labium in two and the clitoris in one patient [1-9]. Most reported cases of vulvar YST were young adults with a median age of 20 years [1-9] (Table 2). Our patient was the eldest case among all the previously reported nine cases. The patient's age and the initial operation type did not seem to have a significant effect on the outcome [1, 3, 4]. A tumor size of 5 cm or less may be a favorable prognostic factor since five of the previous cases have survived with a tumor size 5 cm or less [2, 6-9] whereas neither of the two patients with more than 5 cm tumor size (from the available data) survived [3, 4]. However, the largest reported tumor size was 10 cm but no follow-up information is available [5]. Serum AFP has proven to be a reliable tumor marker for endodermal sinus tumors, especially in patients who had elevated concentrations at the time of diagnosis [7, 11]. Khunamornpong *et al.* recently reported a case and indicated that serum AFP levels may not be a sensitive marker for follow-up of vulvar YST as AFP level did not show any change during the course of the disease (including recurrence) in their patient. However in our patient although serum AFP was within normal limits after the excision of the tumor, with the occurrence of metastasis, it increased from 2.67 IU/ml to 23 IU/ml (0.5-5.5). Serum AFP was evaluated at the initial diagnosis in four cases of vulvar YST [2, 5, 7], two of which had elevated AFPs. There was no elevation of AFP levels in two cases who developed metastasis or tumor recurrence and levels were not stated in the other three cases [1, 3, 4]. Flanagan *et al.* reported a case in which serum AFPs decreased to normal levels five days after vulvectomy and have remained within the normal range [7]. In two of the cases, together with the present case, serum AFP level was normal at the time of the initial diagnosis and elevated with tumor recurrence [8]. The presence of serum AFP elevation at the time of lymph node metastasis in our case may be correlated with the presence of AFP expression in the majority of the tumor cells which was confirmed by immunohistochemical studies.

As for the clinical status of the inguinal lymph nodes at diagnosis, there were three cases with inguinal lymph node metastases including ours [4, 8]. In five of the cases, the inguinal lymph nodes were negative, and in another two the lymph nodes were not palpable.

The best surgical treatment for these patients has been considered controversial [7]. It has been suggested that conservative surgery could be justified and adjuvant chemotherapy and radiation therapy may be beneficial. Chemotherapy with vincristine, actinomycin and cyclophosphamide was the first regimen to show promise with EST [12]. Currently postoperative cisplatin-based chemotherapy (PEB) is the recommended adjuvant chemotherapy for patients with EST with either local or disseminated disease [7, 9, 13]. However, Flanagan *et al.* suggested that radical surgical extirpation rather than conservative surgery followed by platinum-based chemotherapy can be curative. Ipsilateral inguinal lymphadenectomy is also recommended by most authors because inguinal lymph node metastasis was the first evidence of tumor spread outside the vulva in almost all cases [7, 9]. Additionally, lymph node metastasis may occur early in the disease as seen in two of the cases and the present case [8, 9]. Bilateral lymphadenectomy was carried out and no metastatic lymph nodes were found on the contralateral site. The surgical procedures for tumor removal in these patients included excision, wide local excision, and modified radical vulvectomy in the world literature [1-9]. The type of surgery does not seem to effect the outcome of these patients [9]. Although we performed extensive surgery the tumor metastasized in six months in our case. There were three patients out of ten who died of disease although two underwent radical vulvectomy followed by adjuvant vincristine-based chemotherapy and pelvic irradiation.

All of the reported patients with vulvar YST received adjuvant chemotherapy after surgery except for one single case of a two-year-old baby with the smallest tumor reported (1.5 cm) arising in the clitoris [2]. She recovered only with wide local excision of the tumor. Radiation therapy has been thought to be beneficial for long-term disease-free follow-up [9]. It is advised to limit radiation therapy to the vulva and the ipsilateral groin to preserve contralateral ovarian function [6, 9]. Adjuvant radiation therapy to the pelvis was recommended to our patient due to the aggressive clinical course of the tumor and recurrence of the disease in such a short period as six months after the first operation. Radiation therapy was added in four patients with recurrence or metastasis after adjuvant chemotherapy [1, 4, 6, 9]. Among them two of the cases with inguinal lymph node metastases were alive and well after radiation therapy. Our case demonstrates that, although extremely rare, especially in young women with persistent vulvar masses, this highly malignant endodermal sinus tumor must be kept in mind and evaluated promptly. We suggest that radical surgical extirpation followed by chemotherapy, and in recurrent cases radiotherapy, should be the treatment of choice for primary yolk sac tumor of the vulva. As more cases are reported it will be possible in the future to determine the best treatment for this extremely malignant and rare tumor.

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