

Case Report

ASPL-TFE3 Translocation in Vulvovaginal Alveolar Soft Part Sarcoma

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Summary: Alveolar soft part sarcoma of the vulvovaginal region is limited to only 8 reported vaginal cases and 1 vulvar case in the English literature. The histogenesis of the tumor remains intriguing with postulates favoring a myogenic versus nonmyogenic origin. A reciprocal translocation for *ASPL-TFE3* gene fusion, frequently detected in 90% of cases, combined with TFE3 protein immunoreexpression are highly sensitive and specific methods for diagnostic confirmation. The current report describes a unique case of vulvovaginal alveolar soft part sarcoma showing the classic morphologic features with documentation of TFE3 protein expression and the *ASPL-TFE3* gene rearrangement. Furthermore, a brief review of the literature of vulvar and vaginal alveolar soft part sarcoma cases with the various treatment modalities is outlined. **Key Words:** Alveolar soft part sarcoma—Vagina—Vulva—TFE3 protein—*ASPL-TFE3* gene fusion.

Alveolar soft part sarcoma (ASPS) accounts for approximately 0.5% to 1% of all soft tissue tumors and occurs most commonly between the ages of 15 and 35 years with a female preponderance below the age of 25 years. Since its first description, the histogenesis of ASPS has been enigmatic; however, recently, a unique and specific chromosomal rearrangement der (17)t(X;17)(p11;q25) resulting in an *ASPL-TFE3* gene fusion has been identified and implicated in the pathogenesis of this tumor.

ASPS occurs in the lower extremity with 39.5% located in the buttock or anterior thigh compartment.

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Additional rare described locations include mediastinum, breast, urinary bladder, gastrointestinal tract, bone, and the head and neck region, specifically the orbit in children, and the female genital tract. Within the female genital tract, ASPS has been described in the cervix, myometrium, endometrium, and even less commonly the vagina and the vulva (1). The occurrence of ASPS in the vagina is limited to 8 case reports (1–8), and only 1 report describes a vulvar ASPS (9). Herein, a case of ASPS is presented arising within the vulva and involving the vaginal wall in a pregnant patient in which, for the first time for this site, TFE3 protein expression was analyzed along with the corresponding *ASPL-TFE3* gene rearrangement to ascertain the diagnosis.

CASE REPORT

The patient is a 24-year-old G1 P1 LC 1 woman who reported, during the third trimester pregnancy, an asymptomatic 2-cm mass involving the right labium majus and minus. Cesarean section was

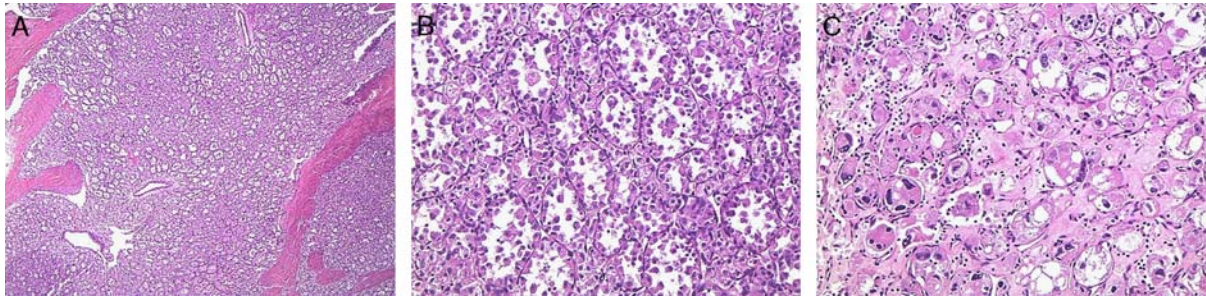


FIG. 1. (A and B) Alveolar soft part sarcoma of the vulvovaginal region with the typical pseudoalveolar growth pattern separated by dense fibrous trabeculae. (C) Focal areas formed of multinucleated and pleomorphic cells with cytoplasmic vacuolization (magnification: 200 ×).

performed without performing a biopsy on the mass. Five months later, the patient re-presented with a 6-cm mass involving the right labium majus, labium minus, and the posterolateral vaginal wall followed by outside referral to the American University of Beirut Medical Center for management. No other gynecologic abnormalities were noted and the inguinal lymph nodes were not enlarged. Computed tomography scan of the brain, chest, abdomen, and pelvis showed no discrete lesions. After wide radical local excision, radiation therapy was administered (6,000 rad) to the tumor bed. The patient shows no evidence of disease 12 months postoperatively.

The excised mass measured 6 × 5 × 4.5 cm, was well-circumscribed, tan-gray, smooth, soft, and homogenous with focal hemorrhage. Histopathologic examination showed nests of loosely cohesive cells separated by thin-walled sinusoidal vascular channels forming a pseudoalveolar pattern and divided by dense fibrous trabeculae. The tumor cells were round to polygonal with focal areas consisting of multinucleated and pleomorphic cells, abundant granular eosinophilic cytoplasm, vesicular nucleus, and prominent nucleolus (Fig. 1). Periodic Acid-Schiff (PAS) stain depicted diastase-resistant crystalline structures

diagnostic of ASPS (Fig. 2). The tumor cells were diffusely positive for TFE3 (monoclonal antibody, clone MRQ-37; Cell Marque) and focally positive for smooth muscle actin (monoclonal antibody, clone 1A4; Dako). Immunohistochemistry (IHC) for CK AE1/AE3 (monoclonal antibody, clone AE1/AE3; Dako), desmin (monoclonal antibody, clone 33; BioGenex), CD34 (monoclonal antibody, clone QBEND/10; Novocastra), HMB-45 (monoclonal antibody, clone HMB-45; Lab Vision), Melan-A (monoclonal antibody, clone A103; Novocastra), S-100 protein (monoclonal antibody, clone 15E2E2; BioGenex), and vimentin (monoclonal antibody, clone V9; BioGenex) were negative. Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed on formalin-fixed paraffin-embedded tissue, as previously described (10), confirming the presence of the *ASPL-TFE3* gene rearrangement (Fig. 3).

DISCUSSION

Vaginal and vulvar ASPS are extremely rare with 8 reported vaginal cases and 1 vulvar case in the English literature (Table 1). The age at presentation

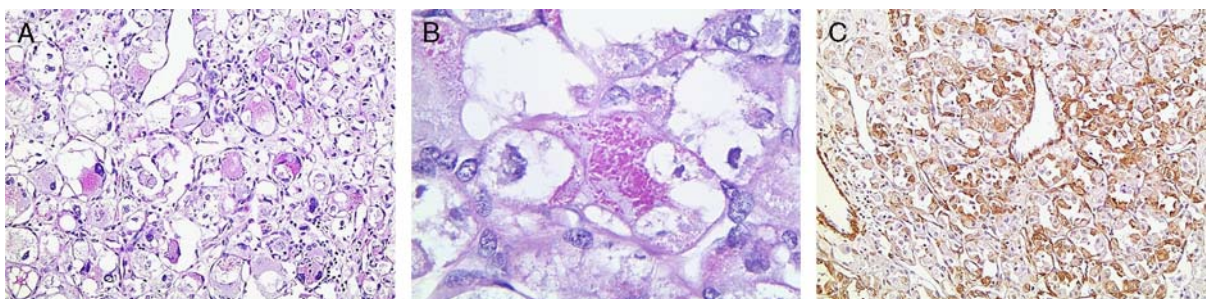


FIG. 2. (A and B) PAS stain revealing the intracytoplasmic, diastase-resistant eosinophilic granules (magnification: 200 ×) appearing as dense crystalline structures (magnification: 1,000 ×) usually identified within foci composed of multinucleated cells. (C) Diffuse cytoplasmic staining for SMA is noted.

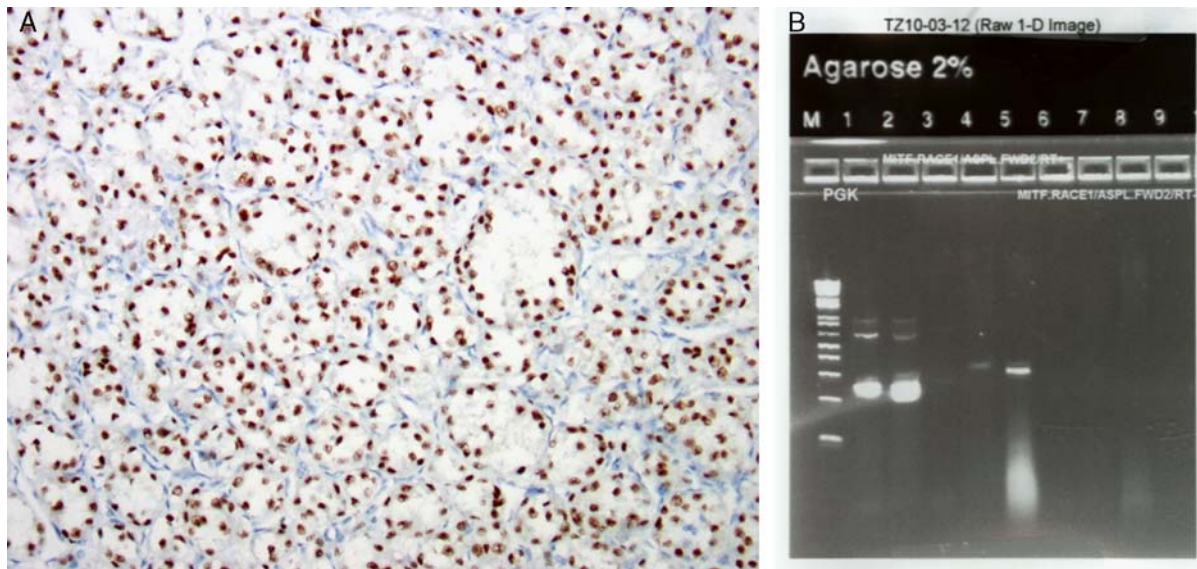


FIG. 3. (A) TFE3 immunostaining diffusely positive in the vulvovaginal ASPS. (B) RT-PCR revealing expression of the *ASPL-TFE3* chimeric gene fusion (Lane 4). Positive (Lane 5) and negative (Lane 3) control tissue for *ASPL-TFE3* gene fusion.

averaged 33 years (range, 18–57 yr old) and the tumor size 5.6 cm (range, 3.0–7.5 cm). The reported clinical presentation was a protruding vaginal mass with occasional bleeding or an asymptomatic labial mass in the case of vulvar ASPS. Similar to the current vulvovaginal ASPS, pregnancy was associated with 2 other vaginal ASPS cases. The disease-free survival period ranged from 2 to 17 years (Table 1). The current case is characterized by the unique combined vulvar and vaginal wall involvement.

Histopathologically, ASPS demonstrates a pseudoalveolar pattern with poor central cohesion. Groups of alveoli are divided by dense, fibrous trabeculae of varying thickness and size. Individual alveoli are separated by vascular sinusoids. PAS stain reveals intracellular glycogen and characteristic, diastase-resistant intracytoplasmic crystalline structures. Ultrastructurally, rhomboid crystals are formed of 4.5- to 5-nm fibers. The tumor cells are usually negative by IHC for NSE, S-100 protein, HMB-45, HHF-35, and vimentin, although positive staining for desmin and SMA is occasionally observed in less than half of ASPS cases involving the uterine cervix (1,11).

ASPS, since its initial depiction, had been postulated to be of myogenic origin (12,13). Gene expression profiling had identified increased expression of muscle-specific B1 integrin binding protein, specifically expressed in skeletal and cardiac muscles (14). An alternative nonmyogenic origin was also proposed

based on the infrequent myogenic marker expression immunohistochemically and through RT-PCR (15,16). In recent years, ASPS has been characterized by a nonreciprocal chromosomal translocation der(17)t(X;17)(p11;q25) forming an oncogenic *ASPL-TFE3* gene fusion (10). *TFE3* gene encodes a protein, member of the microphthalmia transcription family of proteins, involved in cellular proliferation through the kinase pathway (17). *ASPL* gene encodes a protein ubiquitously expressed in adult cardiac and skeletal muscles. The fusion protein is believed to initiate uncontrolled cellular proliferation in ASPS cells.

In the proper clinical context and with the appropriate morphology, IHC for the TFE3 protein and RT-PCR for the detection of the *ASPL-TFE3* gene fusion are highly sensitive and specific methods for the diagnosis of ASPS. The overall sensitivity and specificity of IHC for TFE3 ranges from 91.0% to 97.5% and 99.6%, respectively (18,19). In 1 report, the detection rate for the *ASPL-TFE3* gene fusion in ASPS reached 68.8% (11/16), attributed to the limitation of archival paraffin-embedded formalin-fixed tissue instead of frozen tissue (20). Recently, RT-PCR on paraffin-embedded tissue yielded 24/24 chimeric fusions in ASPS versus 22/24 immunorepression of the TFE3 antibody (21). Previous description of TFE3 protein expression by IHC has been documented in ASPS of the cervix without demonstrating the gene fusion (11). The present case corroborates TFE3 protein expression, in addition to

TABLE 1. Summary of the reported cases of vaginal and vulvar alveolar soft part sarcoma

Case/series	Age (yr)	Tumor size (cm)	Location	Treatment	Follow-up (mo)
Carinelli et al. (2)	27	3	Vagina, left lower 1/3, posterior wall	Surgery + radiotherapy (8,200 rad)	NED (204)
Chang et al. (3)	18	7	Vagina, lower 1/3, anterior wall	Radical surgery + radiotherapy (5,000 rad)	NED (60)
Chapman et al. (4) and Zaleski et al. (5)	26	6	Vagina, right wall, lower 1/3	Surgery + radiotherapy (5,000 rad) + chemotherapy (cisplatin + cytoxan)	DOD (25)
Kasai et al. (1980) (6)	34	7.5	Vagina, right lower 1/3,	Radical surgery	NA
Nielsen et al. (1)	27	Not specified	Vagina, posterior wall	Surgery + radiotherapy (8,200 rad)	NED (204)
	26	Not specified	Vagina, lower 1/3	Surgery + radiotherapy (5,000 rad)	DOD (24)
O'Toole et al. (7)	18	6	Vagina, middle 1/3	Surgery + radiotherapy (4,500 rad)	NED (36)
Tobon et al. (8)	57	Multiple nodules (0.3–0.8)	Vagina, lower 1/3	Surgery	AWD (15)
Shen et al. (9)	62	4	Vulva, right labium minus	Radical vulvectomy with bilateral groin lymph node dissection	NED (24)
Current case	23	6	Vulvovaginal, right labium majus and minus; right lower 1/3, posterior wall	Surgery + radiotherapy (6,000 rad)	NED (12)

AWD indicates alive with disease; DOD, died of disease; NA, not available; NED, no evidence of disease.

the corresponding *ASPL-TFE3* gene rearrangement in other sites of the female genital tract such as the vulvovaginal region.

IHC is helpful in the differential diagnosis of ASPS, which includes clear cell carcinoma, malignant melanoma, paraganglioma, metastatic renal cell carcinoma (RCC), alveolar rhabdomyosarcoma, metastatic adrenal cortical carcinoma and hepatocellular carcinoma, granular cell tumor, and perivascular epithelioid cell tumor (PEComa). Malignant melanoma is HMB-45 and melan-A positive. Paragangliomas are positive for synaptophysin and chromogranin, whereas S-100 protein highlights sustentacular cells. Alveolar rhabdomyosarcomas exhibit skeletal muscle differentiation as demonstrated by muscle markers (myogenin and MyoD-1). Metastatic adrenal cortical carcinomas are positive for inhibin and melan-A, whereas hepatocellular carcinomas are positive for HepPar1. Granular cell tumors lack the PAS-positive crystalline granules and are S-100 protein positive. Clear cell carcinoma of the female genital tract, in comparison to translocation-associated RCC and clear cell RCC, are CK7 positive and CD10/TFE3 negative (22). Clear cell RCCs are CK7/TFE3 negative and CD10/Carbonic anhydrase-IX positive. Some PEComa and translocation-associated RCC are characterized by positive TFE3 staining with a balanced *ASPL-TFE3* chromosomal translocation (22,23); however, PEComa are usually positive for HMB-45 and melan-A. Neoplasms such as granular cell tumor, adrenal cortical carcinoma, high-grade myxofibrosarcoma, and distal common bile duct carcinoma occasionally

express the TFE3 protein by IHC (6/1476 different cases) without a known gene fusion transcript (19). The presence of PAS-positive granules in combination with TFE3 immunostaining and RT-PCR confirmation of the *ASPL-TFE3* gene fusion are helpful diagnostic tools, while confirmation relies essentially on electron microscopy.

Within the female genital tract, ASPS has been reported in the uterine corpus, cervix, vagina, and vulva. ASPS of the uterine cervix and corpus are characterized by an average tumor size of 2.4 cm (range, 0.2–7.0 cm) and 3.9 cm (range, 0.4–9.8 cm), respectively. The majority of patients, both uterine cervix and corpus ASPS, underwent total abdominal hysterectomy with no evidence of disease upon follow-up. Vaginal ASPS tumors were located, similar to the current case, in (7/8) patients within the lower 1/3 of the vaginal wall. Radical surgery with radiotherapy was performed on 5/8 vaginal ASPS cases with 4/8 cases showing no evidence of disease at a mean follow-up period of 126 months (range, 36–204 mo). Tumor size seems to be a critical factor in determining the biologic behavior of upper and lower extremity soft tissue ASPS with a cut-off limit of 5 cm (24,25). Vulvovaginal ASPS cases, as opposed to uterine cervix and corpus ASPS, presented with an average size of 5.6 cm and 2/9 cases died of disease. Tumor size and location, within the female genital tract, seems to dictate the biologic behavior and prognosis of ASPS; however, the paucity of cases and the lack of standardized treatment protocols render conclusive remarks a difficult task. Shen et al. (9) reported a 30% rate of lymph

node metastasis on autopsy cases of ASPs. The role of regional lymphadenectomy is controversial, especially if the index of suspicion is low clinically and radiologically.

ASPs are notorious for brain (incidence of 30%), skeletal, and most commonly lung metastasis. Patients presenting with disseminated disease have poor overall survival with a median of 12 months. γ -knife radiotherapy achieves local brain metastasis control with a progression-free survival of 16 months and a 1-year survival rate of 61% (26). The benefit of additional chemotherapy regimens to metastatic ASPs has minimal efficacy. The conventional chemotherapeutic agents used include gemcitabine, docetaxel, and less efficacious drugs such as doxorubicin, ifosfamide, and dacarbazine.

In conclusion, the unique location of vaginal ASPs raises challenges regarding the diagnosis and treatment of this intriguing neoplasm. However, recently described diagnostic markers such as IHC for the TFE3 protein with RT-PCR detection of the *ASPL-TFE3* gene fusion are highly useful in confirming the diagnosis at this location, as has been the case at other anatomic sites. Despite the large tumor size (> 5 cm), wide local excision with concomitant radiotherapy seems to have short-term local disease control based on the limited published literature.

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