

Case Report

Primary alveolar soft part sarcoma of the uterine cervix: a case report and literature review

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Abstract: Alveolar soft part sarcoma (ASPS) is a tumor of unknown histogenesis, composed of large, epithelioid cells with eosinophilic cytoplasm, having an alveolar pattern. Primary ASPS of uterine cervix is very rare. In this report, we present a 21-aged-old female with primary ASPS in the uterine cervix and discuss the clinicopathological characteristics, immunophenotype, molecular genetic feature and differential diagnosis of ASPS of cervix.

Keywords: Alveolar soft part sarcoma, tumor, uterine cervix

Introduction

ASPS forms less than 1% of all the soft tissue sarcomas [1]. Its histogenesis is unclear. Primary ASPS of uterine cervix is very rare. Only about 10 cases with primary involvement of the uterine cervix have been reported previously in china. It is easily misdiagnosed as other diseases, which might lead to different following therapy. Because of the rarity of the disease, to raise awareness of this disease, we reported a case and performed a detailed literature review.

Case report

A 21-aged female, presenting with increased menstrual bleeding in 2 years duration, received treatment in our hospital 4 months ago. A hypoechoic mass occupying 3.0 cm×2.6 cm×3.4 cm in cervical canal was revealed through transvaginal color doppler ultrasound, with well-defined boundary and fluent blood flow nearby. The cervical tumor resection under hysteroscope was performed. There was an exogenous 5 cm×4 cm×4 cm mass near internal cervical os, with a thin pedicle. There was no abnormality in uterus corpus.

Gross examination of the cervical tumor showed grey yellow and off-white unshaped tissues that measured 5 cm×4 cm×3 cm, and the

texture was homogeneous and soft. Microscopic examination revealed the tumor was under the cervical mucosa, the tumor invaded into the stroma focally though the tumor border was clear in most areas. The tumor cells arranged in organ-like, alveolar or nest-like growth pattern, and were separated by fibrovascular septa. The tumor cells showed uniformly round and polygonal appearance with distinct borders usually. The cytoplasm was abundant and eosinophilic, and the nucleus was oval, with obvious nucleolus and mitosis was rare (**Figure 1**). The immunohistochemical staining exhibited positivity for TFE3 (**Figure 2**), myoD1 (cytoplasm), myogenin (cytoplasm), MSA, CD68 and Ki-67 (3%), focally positivity for for NSE, while negativity for vimentin, Pan-CK, EMA, desmin, HMB45, melan-A, S-100 and CgA. The periodic acid Schiff staining with diastase treatment (D-PAS) showed red needle crystals in cytoplasm (**Figure 3**). Red and green fluorescence fusion signals were found in more than 70% in tumor cells by Fluorescence in situ hybridization (FISH) test (**Figure 4**), which demonstrated the fusion of TEF3 gene and ASPL gene resulted by der(17)t(X;17)(p11;q25). The probes were purchased from Empire Genomics company, including TFE3 gene in X chromosome labeled with red fluorescence (Rp11-416B14, Rp11-344N17) and ASPL gene in chromosome 17 labeled with green fluorescence (Rp11-655F9, Rp11-765014).

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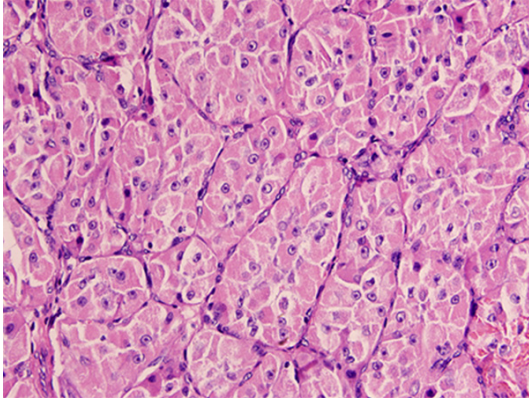


Figure 1. The tumor cells arrange in alveolar pattern, with fibrovascular septa, and have distinct border, eosinophilic cytoplasm, and nuclei in the middle with prominent nucleolus (HE×400).

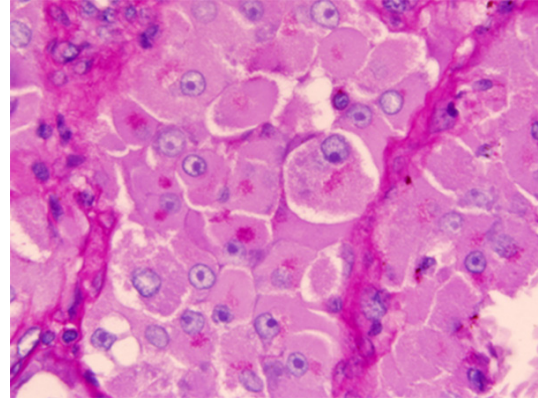


Figure 3. Red needle crystal is seen in cytoplasm of tumor cells after D-PAS stain (×1000).

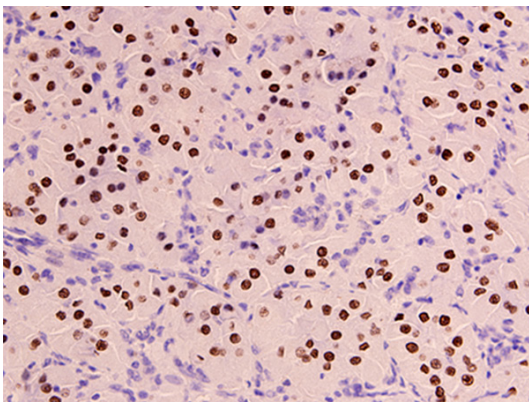


Figure 2. The nuclei of tumor cells are positive for TFE3 (EnVision ×400).

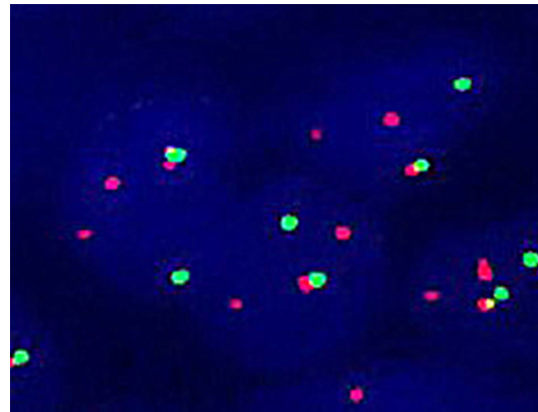


Figure 4. ASPL-TFE3 fusion gene is detected in tumor cells (red and green fusion fluorescence) (×1000).

Then, the diagnosis of alveolar soft part sarcoma (ASPS) of the uterine cervix was confirmed. Thereafter the patient received transabdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection. No ascites or abnormal appearance of uterus corpus and bilateral adnexa was observed during operation. On postoperative pathological examination, there was no residual tumor in uterus and no tumor metastasis in pelvic and para-aortic lymph node was observed. The patient didn't receive other treatments and no evidence of tumor recurrence or metastasis was found in follow-up of 3 months.

Discussion

ASPS is a kind of rare malignant soft tissue tumor, the incidence of which accounts for about 0.5-1% of soft tissue tumors and the true origin has not been clear yet. ASPS is more

common in young people particularly in those who aged 15-35, and 60% are in females [1]. The common sites are trunk and limbs, especially the deep soft tissues of thigh and buttock [2]. In children and infant, the common sites are head, neck region, orbit and tongue [3]. ASPS in other rare sites, such as lung, mediastinum, peritoneum, sinus, stomach, breast, uterine cervix and heart, also has been reported [4]. ASPS is a slow-growing and long-course tumor and rarely recurs if clearly excised. However, ASPS is prone to blood metastasis in early stage with a transfer rate of 50% [5]. Lungs are the most common metastatic site, followed by brain, bones and livers.

Primary ASPS of uterine cervix is very rare [6]. Flint et al. firstly reported about primary cervical ASPS in 1958 [7]. At present, there are only about 10 cases reported in China. Behaved similarly with ASPS in other parts, most cervical ASPS are slow-growing and painless mass with

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clinical character of irregular vagina bleeding, while some cases are found occasionally while operating total hysterectomy. So it is hard to make a definite diagnosis about early-stage ASPS of uterine cervix. The cervical ASPS tumor was 0.1 cm-4 cm in diameter, smaller than ASPS in other parts. The reason might be related to the tumor growth in uterine cervix. In general, borders of tumor were clear; nodular and infiltrative growth rarely happened. This was different with other soft tissue sarcoma appeared in female genital tract [8]. Most of the tumors were not encapsulated completely, characterized in grey yellow or off-white section and fish-meat like appearance. Larger tumors may present bleeding, necrosis and cystic degeneration. Findings under microscopic examination were the same as ASPS in soft tissue. Tumor was separated into different sizes of nest-like or alveolar-like structure by slender fibrovascular septa. Tumor cells inside the nest-like mass became alveolar shape because of bad cell adhesion, and partly could be solid. Under high power field, the following features can be seen: clear cell borders, uniform shapes (round, oval or polygon), abundant eosinophilic granular cytoplasm, different size of nucleus (mononuclear or binuclear) with prominent nucleoli, and rare mitosis. Tumor embolus was often observed in tumor vessel, indicating that blood metastasis was easy to occur in early stage of this disease.

Specific stain and immunohistochemical stain had significant supporting role in diagnosing ASPS. Tumor cells partly cytoplasmic expresses MyoD1, with 40% cases of desmin positive and 20%-30% cases of SMA focally positive, while the epithelial marker usually negative. Red rod-like or needle-like crystal was observed in cytoplasm by PAS stain and D-PAS stain [6], with a positive rate of 80% [5], which had certain specificity for ASPS diagnosis. Besides, TFE3 was regarded as very useful marker for ASPS diagnosis, which located in the short arm of X chromosome, and might take part in many gene regulations. Half-life period of TFE3 transcription factor was short with low expression level, so it was hard to detect the wide type TFE3 protein inside the cell nucleus by immunohistochemistry [9]. Specific der(17)t(X;17) (p11;q25) could be detected among about 90% of ASPS cases. This unbalanced translocation caused gene fusion between TFE3 gene and ASPL gene resulting over-expression or decreased degradation of TFE3 fusion protein, and nuclear expression of TFE3 could be

detected by immunohistochemistry [9-10]. Immunohistochemical TFE3 antigen detection and RT-PCR for ASPL-TFE3 fusion gene mRNA detection were performed on 18 cases of ASPS (one of them was primary cervical tumor) and 25 control cases by Williams et al. in 2011 [11]. The result showed TFE3 antigen and ASPL-TFE3 were all positive among 18 cases while fusion gene in 25 control cases were all negative. Only 5 control cases of TFE3 antigen detection were positive. Nuclear expression of TFE3 and ASPL-TFE3 fusion gene were detected in this case; thus, immunohistochemical stain for TFE3 antigen and RT-PCR or FISH detection for ASPL-TFE3 fusion gene were effective indicators for diagnosing ASPS.

There have been lots of views about the origin of ASPS. ASPS expressed MyoD1 partly, and rod-like or needle-like crystalline, which was similar with actin in structure [12], could be observed in cytoplasm through ultrastructure observation. All these characteristics were regarded as strong evidences to support that ASPS might derive from striated muscle. But more studies indicated that expression of MyoD1 in ASPS was lower than 50% and located in cytoplasm. Meanwhile, myogenin was often negative [12]. In addition, ASPS could partly or focally express neurogenic marker, so the view of striated muscle-derived couldn't be fully supported. It was still classified into tumor of unknown origin of tumor in WHO Classification of Tumors of Soft Tissue in 2013 [13]. The confirmation of origin of ASPS still needs further study.

ASPS has typical alveolar structure under light microscopy, but due to the low incidence, non-characteristic clinical manifestation, and untypical location, it is easily misdiagnosed as other diseases, which might lead to different following therapy. The main differential diagnosis are as followed: (1) The alveolar rhabdomyosarcoma is often seen in teenager, and the tumor cells often arrange in nest-like or alveolar pattern, but lacks of fibrovascular septa. The tumor cells strongly express desmin, myogenin and MyoD1. (2) The tumor cells of granular cell tumor often arrange in sheet without alveolar structure. The tumor cells usually has one small and round nucleus located in center. The cytoplasm was abundant, eosinophilic and granular. The immunohistochemical staining of S-100 was positive. (3) The tumor cells of paragangliocytoma were separated by thin-wall sinus blood vessel forming an organ-like pattern. It extreme-

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ly rarely occurred in cervix. Immunohistochemistry shows a layer of sustentacular cells showing S-100 positivity embrace the nest-like tumor cells showing Syn and CgA positivity. (4) Cervical adenocarcinoma presented cribriform, papillary and true tubular distribution, and expressed epithelial markers.

Extrascial total hysterectomy is recommended for the treatment of primary cervical ASPS in most cases. The radiotherapy has no obvious effect on increasing patient's survival rate but can be regarded as postoperative adjunctive therapy [14]. As for the removal of adnexa and pelvic lymph node dissection, the patient's age and reproductive desire should be taken into comprehensive consideration. From present cervical ASPS cases that had been reported, prognosis of ASPS in female genital tract was better than that of other parts. Fadare [6] once had 9-192 months follow-up visits to 10 cases of primary cervical ASPS (48 months on average), and no metastasis or recurrence was observed.

In conclusion, primary cervical ASPS is a very rare malignant mesenchymal tumor, which shows up as irregular vagina bleeding or painless cervical nodule. The histological feature is its alveolar structure, and nuclear expression of TFE3 and ASPL-TFE3 fusion genes detection are positive. Diagnosis of primary cervical ASPS depends on pathological examination. Main treatment is total hysterectomy simply accompanied by radiotherapy. Prognosis of ASPS in female genital tract is better than that of ASPS in other parts.

Disclosure of conflict of interest

None.

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