Case Report
Alveolar soft-part sarcoma of the prostate: a case report and review of the literature

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Abstract: Alveolar soft-part sarcoma (ASPS) is a rare malignant soft tissue tumor of uncertain cellular origin. We reported the case of a 21-year-old man with ASPS presenting itself as a markedly vascular tumor of the prostate. Immunohistochemistry showed positive nuclear staining for TFE3, positive cytoplasm staining for MyoD1 and neuron-specific enolase, and negative for S100, CK, synaptophysin, chromogranin A, myogenin and PSA. A dual-color, break-apart fluorescence in situ hybridization (FISH) assay identified the presence of a TFE3 gene fusion in the tumor cells. RT-PCR was performed to confirm the ASPSCR1 (ASPL)/TFE3 fusion transcript product in the tumor tissue. The patient suffered bone metastases 8 months after surgery and died of cachexia 14 months later. ASPS of the prostate should be discussed in terms of differential diagnosis from clinicopathological characteristics, immunophenotypes, and molecular genetic features.

Introduction

Alveolar soft-part sarcoma (ASPS) was first described in 1952 [1]. Primary ASPS of the prostate is very rare. Because it has a close clinical and histologic resemblance to other tumors such as paragangliomas, rhabdomyosarcomas and granular cell tumors, there is a danger of misdiagnosis and therefore inadequate or delayed treatment. In order to raise awareness of this disease, we present a case and perform a detailed literature review.

Case report

A 21-year-old man was admitted to our hospital due to frequent micturition, urinary urgency and dysuria. He suffered from abdominal pain for 2 months and had recently had a fever. Hypertension and diabetes were not present in the patient, and he had no family history of urinary cancer. An enlarged prostate gland, which was tender and hard, was observed in a digital rectal examination. Prostate-specific antigen levels were normal. Computed tomography (CT) and magnetic resonance imaging revealed a large, multilobulated, partially ill-defined, and heterogeneous mass with a size of 8.4 cm × 7.4 cm × 6.5 cm in the presacral space with multiple little cystic changes in the prostate, infiltrating to the trigon of the bladder. A moderate amount of peritoneal effusion was also found. The cancer antigen 125 level was 209.15 U/mL.

Subsequently, the patient underwent an ultrasound-guided transrectal prostate biopsy followed by a transurethral cystoscope examination. The cystoscope found in the bladder neck a neoplasm 2 cm in diameter which was spherical, pedicle, and the surface of which was congested and necrotic. Each side wall of the bladder was congested and few other neoplasms were observed. A bladder neck biopsy was also performed.

Many pseudo-alveolar or nesting patterns were found by microscopy in the prostate and the bladder neck. Most of the vascular channels were enclosed by thin connective tissue septa.
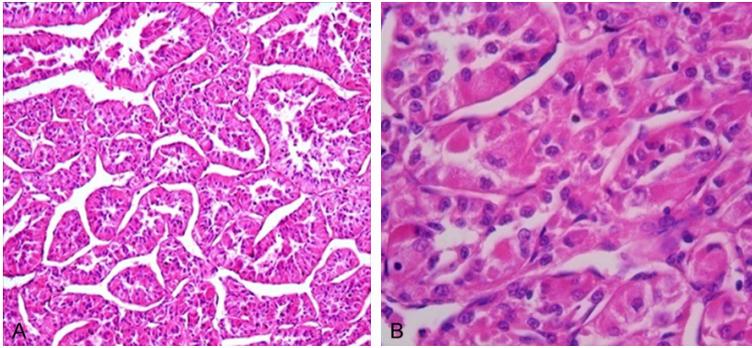
Figure 1. Histology of alveolar soft-part sarcoma. A. An area showing an organ-like pattern in the prostate (H&E, 200 ×). B. Tumor cells in the prostate with abundant eosinophilic cytoplasms, which are somewhat granular. Mitotic figures are uncommon (H&E, 400 ×).
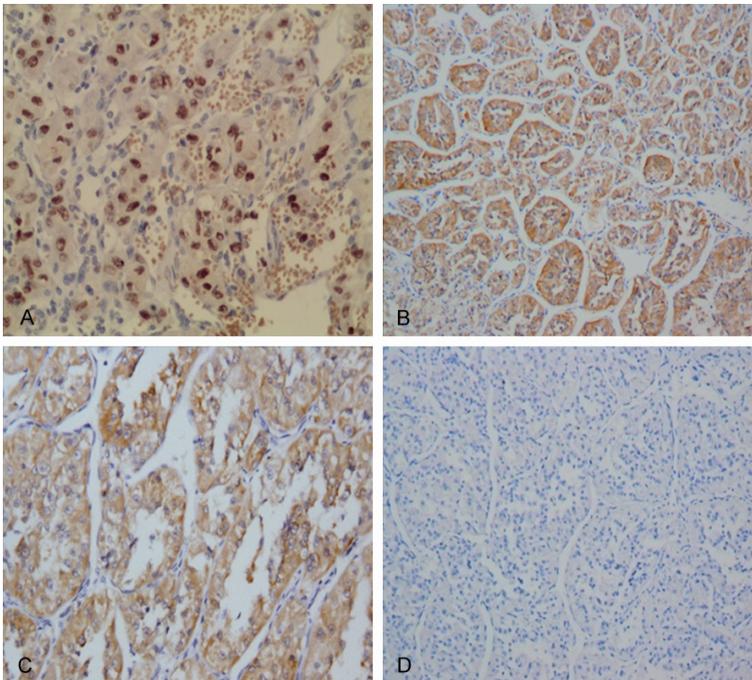

Figure 2. A. Tumor cells show diffuse nuclear positivity. B. Diffuse cytoplasmic staining with NSE. C. Cytoplasmic staining with MYOD1. D. Negative staining for S100.

The tumor cells had abundant eosinophilic cytoplasms and large vesicular nuclei containing prominent nucleoli. The tumor cells had minor dysplasia with uncommon mitotic figures. Immunohistochemical staining revealed that the tumor cells were positive for neuron-specific enolase, weak staining for chromogranin A, but negative for S100, epithelial membrane antigen, cytokeratin (CK), synaptophysin, inhibin-A, smooth muscle actin (SMA), desmin, P504s, and PSA, which is suggestive of a paraganglioma.

The patient underwent a radical prostatectomy, a radical bladder cystectomy and a bilateral urinary diversion. A parenchymatous prostatic neoplasm with a sallow gray-red section and delicate texture was found by gross examination. The size of the tumor was about 8 cm × 7 cm × 6 cm. Part of the tumor invaded the bladder neck.

Microscopic examination revealed that the polygonal tumor cells with eosinophilic cytoplasms were delineated by thin fibrovascular separation which separated the tumor cells into an organoid or nest-like pattern. The tumor cells were large and polyhedral with small and rounded nuclei (**Figure 1**). Immunohistochemistry showed positive nuclear staining for TFE3, positive cytoplasm staining for MyoD1 and neuron-specific enolase (**Figure 2**), negative for S100, epithelial membrane antigen, CK, synaptophysin, chromogranin A, Myogenin, HMB-45, and PSA. Diastase-resistant PAS staining was negative in the tumor cells in this case.

A fluorescence in situ hybridization (FISH) assay identified the presence of a TFE3 gene fusion in the paraffin-embedded tissues. The transcription factor gene (TFE3) of the X chromosome fused with chromosome 17, and the aberrant fusion protein ASPL-TFE3 was largely distributed in the tumor cells (**Figure 3**).

The probes were purchased from Empire Genomics Company, including the ASPL gene labeled with green fluorescence (Rp11-655F9, Rp11-765014) and the TFE3 gene labeled with red fluorescence (Rp11-416B14, Rp11-344N17). A TFE3 FISH assay of the tumor cells showed 1 set of fusion signals and 1 set of green and red split signals observed in approxi-
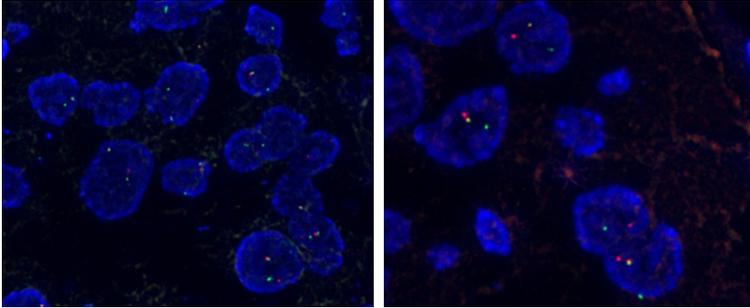
Figure 3. The fusion pattern observed by FISH is an unbalanced X; 17 translocation with the gain of a normal X chromosome (red and green fusion fluorescence). A TFE3 fluorescence in situ hybridization assay showed 1 set of fusion signals and 1 set of green and red split signals, indicating evidence of a TFE3 gene rearrangement.

Discussion

In 1952, Christopherson reported 12 cases of malignant soft tumor with an acinar-like or organ-like pattern separated by fibrous blood vessels, called alveolar soft tissue sarcoma [1]. ASPS was reported as a rare, slow-growing, indolent soft tissue sarcoma with early metastasis and relapse.

Generally, ASPS accounts for approximately 0.5-1% of all soft tissue sarcomas and affects mainly adolescents and young adults [2], with female predilection. It largely affects the deep soft tissue. A few cases may occur in the female genital tract, breasts, shoulder blades, the tympanic cavity, nasal cavity [3-6] and other parts. This case was a rare site of ASPS, occurring in the prostate and involving the bladder. Few such cases have been reported in the English literature.

mately 20% of the tumorous nuclei, indicating the presence of a TFE3 gene rearrangement.

To detect ASPSCR1/TFE3 fusion, a reverse-transcription polymerase chain reaction (RT-PCR) was performed. Total RNA was extracted from the paraffin-embedded tumor tissues. The primer sequences used are as follows: ASPL-E7-F3: TCCAAGCCAAAGAAGTCCAA; TFE3-E6-R2: GCCACGCCTTGACTACTGTAC. DNA sequencing of PCR products was performed using a Qiagen 3000 BioRobot (Qiagen, German). Written, informed consent was obtained from the patient. A sequence analysis showed that there was an unbalanced translocation of Chromosome 17 and the X chromosome (**Figure 4**), and that the ASPL-TFE3 fusion product was 146bp long (Structurally, exon 7 of the ASPL gene is fused with the TFE3 gene at exon 6). The patient was therefore finally diagnosed as having ASPS.

Two months after the surgery, followed by informed consent, the patient started a soft tissue sarcoma chemotherapy protocol of epirubicin 50 mg iv with ifosfamide 1000 mg iv (day 1) and cisplatin 40 mg iv (day 2). The patient received 4 cycles of chemotherapy for 4 months.

Unfortunately, 2 months later, 8 months after surgery, an abdominal CT scan showed that there were soft tissue shadows in the prostate surgery areas, with multiple soft tissue nodules in the abdominal omentum and mesentery. There was left ischial bone destruction, which indicated a strong possibility of metastases. The patient died of obvious cachexia 22 months after the surgery.

With a slow, insidious growth, ASPS is often discovered by accident. The tumor's size can sometimes be up to 6~10 cm in diameter. ASPS relapses easily (the local recurrence rate can be up to 20%) [7]. As a rule, ASPS is richly vascular. Widely hematogenous route transfer occurs mainly in areas such as the lungs, bones, brain, and skin [2]. With a propensity for early metastatic spread, ASPS occurring outside of the head and neck frequently presents itself as a large mass.

Gross examination shows that ASPS is generally nodular. The tumor may have a false capsule and poor border, ranging in size from 1 to 24 cm. ASPS tends to be gray brown in color and have a soft, flesh texture. Larger lesions are often accompanied by bleeding necrosis and cystic degeneration. Microscopically, different parts of the tumor morphology are slightly different. Through low-power observation, the most characteristic histological appearance of ASPS is an organoid or nesting pattern. Cell nests tend to be uniform but may vary in size and shape. Tumor cells in the center of nests lack adhesion, and necrosis may form a false alveolar structure. In some cases, especially in infants and children, the tumor cells may appear to have a more diffuse growing pattern instead of an obvious nest-like structure.
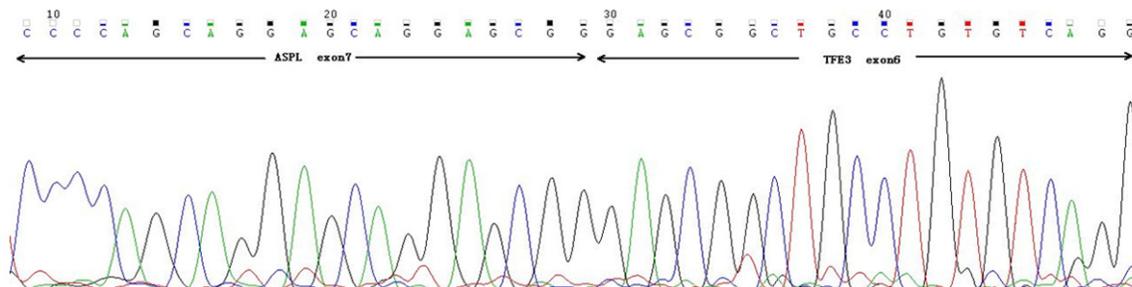
Figure 4. RT-PCR and gene sequencing findings: identification of the ASPSCR1 (ASPL)/TFE3 fusion transcript product in the tumor tissue.

The tumor cells are large and polygonal or round with small differences in size and shape, containing one or two vesicular nuclei with prominent nucleoli. Nuclear atypia may exist but are uncommon. Mitotic figures are not easily seen.

ASPS tumor cells have abundant eosinophilic granular cytoplasms, which are partially transparent or vacuolar. The cells frequently contain rhomboid or rod-shaped intracytoplasmic inclusions which may be faint in HE staining but can be better observed with PAS staining after diastase digestion. The number of inclusions in different cases is quite different. In some cases, these inclusions are visible within most tumor cells, but in others they may also be rare or even absent.

TFE3 staining is extremely helpful in confirming the diagnosis of ASPS. The TFE3 immunoglobulin heavy chain gene is located at the sub-mu-E3 enhanced sequence, the translocation of which can lead to abnormal expression of TFE3 protein.

ASPS is usually negative for cytokeratins, epithelial membrane antigen, synaptophysin, chromogranin and HMB-45.NSE, with S100 and desmin being occasionally positive.

The origin of ASPS still remains obscure. Currently, more evidence supports a myogenic origin. Ultrastructure observation shows that in ASPS, fine granular and crystal rods of diagnostic significance can be seen in the cytoplasm, and the crystals' structure is similar to actin [8]. Immunohistochemical studies have shown that actin, desmin, and other related markers have different degrees of expression in ASPS [9]. Molecular biological studies suggest that muscle regulatory proteins, such as a-actin mRNA, can be expressed in ASPS [10].

Although strong TFE3 immunoreactivity is always essentially presented in ASPS, a few cases may be negative. Martignoni et al. [11] found two cases (from a total of 24 cases) of ASPS without TFE3 expression, but the ASPL-TFE3 gene fusion was detected by FISH. Therefore, for atypical cases, FISH detection of TFE3 gene rearrangement is now the preferred method [12, 13].

Recent genetic studies reveal that ASPS exhibits a conserved aberration in the form of an unbalanced translocation der(17)t(X;17)(p11;q25) [14]. This translocation fuses the N-terminal region of the ASPL gene at 17q25 to the C-terminal region of transcription factor TFE3, which is located at Xp11 [15].

Currently, the RT-PCR assay is considered the most powerful tool available for identifying ASPS. Two variants of ASPSCR1/TFE3 gene fusion have been observed in the expression of two distinct fusion transcripts, ASPL-TFE3 type 1 and type 2 [15-17]. The presence of two X chromosomes in females enhances the chances of translocation on this chromosome, thereby explaining the female predilection [18].

Differential diagnosis

A reliable diagnosis of ASPS can be performed according to the clinical features, histological appearances, and genetics. It should be differentiated from the following diseases using differential diagnosis.

Paraganglioma

It most typically occurs in the elderly, with no gender predilection. Most paragangliomas are single and sporadic, though a few cases with family history often present themselves as multiple nodules. It often occurs in the head and

neck, mediastinal and retroperitoneal, which are chemoreceptor sites.

Histologically, the tumor cells are separated by thin-wall sinus blood vessels forming an organ-like pattern. Tumor cell nests are smaller and uniform; the surrounding cells are flat sustentacular cells. The tumor cells are smaller with eosinophilic cytoplasms and smaller particles in contrast to ASPS. Immunohistochemistry shows a layer of sustentacular cells showing S-100 positivity which embrace the nest-like tumor cells showing NSE, Syn and CgA positivity, while desmin, MyoD1, and MSA stain negative. Electron microscopy shows that the tumor cells have neuroendocrine granules.

Alveolar rhabdomyosarcoma

Tumor cells show a nest-like or alveolar pattern, with fibrovascular stroma between the alveoli. There is a lack of an antral vascular network. The tumor is composed of round, ovular, small polygonal primitive mesenchymal cells and the scattered eosinophilic cytoplasms of immature rhabdomyoblasts. The tumor cells strongly express desmin, myogenin, MyoD1, and MSA.

Granular cell tumor (GCT)

GCT is more common in the elderly, generally located in the head and neck, limbs, trunk of the skin and subcutaneous tissue, and measures less than 3 cm in size. The microscopic picture of GCT shows that the tumor cells are arranged in flakes, clusters or nests, with the lack of a stroma sinus. Tumor cells have small and round nuclei located in their centers. The cytoplasms are abundant, eosinophilic and granular. Prominent nuclear immunoreactivity for TFE3 can also be seen in some granular cell tumors [19]. However, the immunohistochemical staining of S-100 and NSE is positive, but this is thought to come from Schwann cells. SMA, desmin and keratins stain negative.

Metastatic adenocarcinoma containing rich blood vessels

ASPS, having an alveolar structure with abundant cytoplasms, epithelioid, is often misdiagnosed as liver, kidney and adrenal metastasis adenocarcinoma. However, the intermediate cells in the nests of ASPS are looser and the acini lumen margins are irregular, unlike the real lumen of glands - the acini lumen edge of metastatic adenocarcinoma is neat. CEA, EMA, and CK stain positive, with the absence of a D-PAS stain in cytoplasmic crystalline particles. The Xp11.2 translocation associated with RCC harbors a balanced t(X;17)(p11.2;q25) translocation in most cases, which can contrasted to that of ASPS [20, 21].

The treatment of choice for ASPS is generally surgical excision with sufficient margins supplemented by adjuvant chemotherapy and radiotherapy. However, the effectiveness of adjuvant chemotherapy and radiotherapy is inconclusive. Local recurrence and metastasis of the tumor tends to be resistant to radiation and chemotherapy. Therefore, patients need long-term, postoperative, regular follow-ups. Recently, new molecular target therapies under study [22, 23] may change the natural course of the disease as well as possible approaches to primary disease in the near future.

ASPS can demonstrate early hematogenous metastases. Hence, early detection of the primary tumor and extensive tumor resection is the key point to the treatment. The prognostic parameters of ASPS include age at the time of diagnosis, tumor size, AJCC stage and the presence of metastases at the time of diagnosis [4, 24]. Cases with recurrence, metastasis and incomplete removal have a poor prognosis. There is a significant correlation between tumor size and the presence of metastases [24]. In Koichi's study, 12 of 15 patients (80%) with tumors measuring > 5 cm in diameter demonstrated metastatic disease (AJCC stage IV) (P = 0.001). In this report, the 21-year-old male with tumor size larger than 7 cm was found with bone metastases 8 months after the complete tumor excision.

Conclusion

In conclusion, we report a case of ASPS arising from the prostate, which is an extremely rare location. TFE3 immunoreactivity, the immunohistochemical panel, FISH and RT-PCR for the ASPL-TFE3 fusion transcript characteristic of the t(X;17) are very useful for the differential diagnosis of ASPS.

Disclosure of conflict of interest

None.

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