

# Second Reported Case of Pediatric Bladder Alveolar Soft Part Sarcoma as Secondary Malignancy After Prior Cytotoxic Chemotherapy

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Alveolar soft part sarcoma (ASPS) is a rare malignancy with high rates of metastasis at presentation, defined by an unclear cellular origin and a unique unbalanced ASPSCR1-TFE3 translocation (der(17)t(X:17)(p11;q25)).<sup>1</sup> ASPS is insensitive to chemotherapy and has been reported to involve the bladder only twice in the pediatric literature; once as a primary malignancy,<sup>2</sup> and once as a secondary malignancy after cytotoxic chemotherapy.<sup>3</sup> Herein, we report the third case of pediatric bladder ASPS in a female patient who received cytotoxic chemotherapy for low-risk neuroblastoma. This would represent the second case of pediatric bladder ASPS as a secondary malignancy after prior chemotherapy. UROLOGY 00: 1–3, 2019. © 2019 Elsevier Inc.

**A**lveolar soft part sarcoma (ASPS) accounts for only 0.5%-1% of all reported soft tissue sarcomas.<sup>4</sup> ASPS classically occurs in the extremities in adults and often involves the head and neck in the pediatric population.<sup>4</sup> Surveillance Epidemiology End Results Registry data reveals only 251 patients diagnosed with ASPS in the past 51 years.<sup>5</sup> ASPS is considered resistant to both chemotherapy and radiation.<sup>1,6</sup> ASPS rarely affects the genitourinary tract. Herein, we report the second case of pediatric bladder ASPS in a patient who received prior chemotherapy, and the third known case of pediatric bladder ASPS.<sup>2,3,7-9</sup>

## CASE REPORT

A 9-year-old female presented to our emergency department with hematuria, dysuria, and decreased urine volumes. Her urinalysis revealed RBCs and WBCs and was otherwise unremarkable. Ultrasonography demonstrated normal kidneys and a 4 cm mass at the left bladder wall. Computed tomography revealed a 4.2 × 3.8 × 3.2 cm enhancing mass involving the left bladder wall without obvious lymphadenopathy (Figs. 1 and 2).

The patient's history was significant for stage 4S neuroblastoma of the neck diagnosed at 9 months of age, treated with 2 cycles of chemotherapy per COG ANBL0531

protocol for low-risk neuroblastoma (cycle 1: carboplatin and etoposide, cycle 2: carboplatin, cyclophosphamide, and doxorubicin). Initially, this mass raised concern for recurrence of neuroblastoma, however metabolic workup, whole body positron emission tomography (PET), and metaiodobenzylguanidine scan resulted negative. After multidisciplinary tumor board discussion, the patient underwent surgical excision for diagnostic purposes.

Extraperitoneal open cystotomy was performed, revealing no obvious extravesical disease, and the mass was easily excised off its stalk. Frozen section was suggestive of low-grade neuroendocrine tumor. The patient's urinary complaints were likely related to a "ball-valve" phenomenon by the mass causing bladder neck occlusion.

Sections of the specimen demonstrated nests of large polygonal cells with eosinophilic granular cytoplasm separated by a delicate fibrovascular stroma, and round central nuclei and prominent nucleoli. No mitotic figures or tumor necrosis was identified. Immunohistochemical studies were positive for periodic acid-Schiff (PAS) crystals, smooth muscle actin, INI1, and TFE3, and were negative for CD34, CD56, CD68, chromogranin, synaptophysin, CK AE1/AE3, GFAP, S100, desmin, HMB45, melan-A and myogenin.

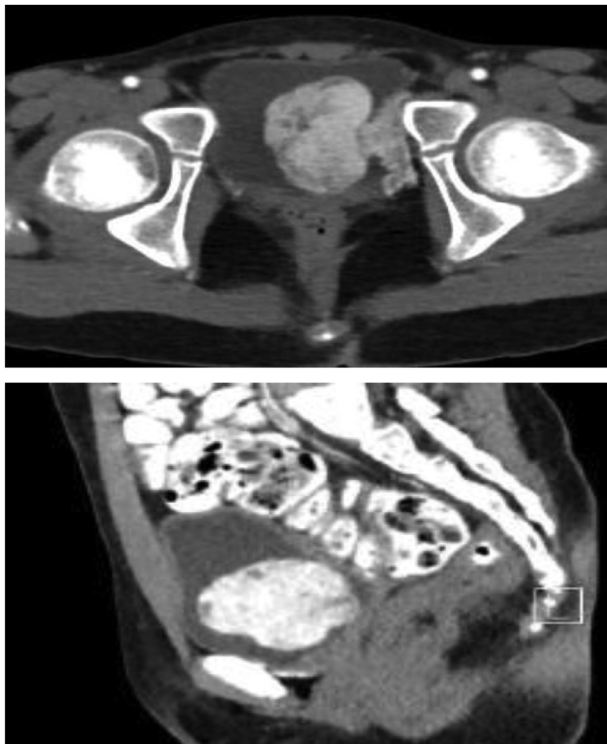
Based on presence of classically described histologic findings,<sup>4</sup> positivity of TFE3, and exclusion of common bladder tumors, ASPS diagnosis was made. After recovery, the patient returned for partial cystectomy and bilateral pelvic lymph node dissection with achievement of negative margins. Final pathology returned pT1, with no lymph node involvement. One month postoperatively the patient's voiding habits returned to normal without need for anticholinergics.

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**Figure 1.** Axial and sagittal images reveal 4.2 cm enhancing left lateral bladder mass.



**Figure 2.** 4.2 cm pedunculated left lateral bladder wall mass excised off thin stalk for diagnostic purposes. (Color version available online.)

The patient is now 7 months removed from definitive resection without recurrence on imaging. No adjuvant therapy is planned at this time after multidisciplinary discussion. A multigene hereditary cancer panel was negative. She will continue to follow-up for close surveillance imaging moving forward.

## DISCUSSION

Herein, we report a 9-year-old female with bladder ASPS as a second primary malignancy after receiving low cumulative doses of chemotherapy as an infant. ASPS represents <1% of soft tissue sarcomas and typically affects patients 15-35 years old.<sup>4</sup> It most often involves the lower extremities, followed by chest/trunk and upper extremities. Involvement of the head and neck is more common in children.<sup>6,10-12</sup> There have been 6 reported cases of bladder involvement to date.<sup>9</sup> ASPS usually has an indolent course, but has a high rate of metastasis at diagnosis (20%-40%).<sup>13,14</sup> Prior studies demonstrate a 71% 5-year survival rate for localized disease compared to 20% in patients with metastatic disease, however a recent prospective trial noted 100% 5-year survival after resection of localized disease.<sup>4,6</sup>

Histologically, tumors characteristically contain cells with periodic acid–Schiff, diastase-resistant rhomboid/rod-shaped crystals with loss of central adhesion.<sup>4</sup> ASPS is characterized by translocation of the X chromosome and chromosome 17, creating a fusion of transcription factor E3 (TFE3) located at Xp11 with the ASPS critical region 1 (ASPCR1) at 17q25, resulting in activated tyrosine-protein kinase-Met (MET) signaling promoting angiogenesis and proliferation.<sup>4</sup> This unique translocation is identical to Xp11 translocation-associated pediatric renal cell carcinomas (RCCs), as well as secondary malignancies including acute leukemias and perivascular epithelioid cell tumors.<sup>3</sup> TFE3 positivity is pathognomonic for ASPS and Xp11 translocation RCC.<sup>8</sup>

ASPS tumors are highly vascular, thus the use of anti-angiogenic agents has increased with promising albeit early results.<sup>6,14,15</sup> Complete surgical resection remains standard of care for ASPS, as it is thought resistant to conventional chemotherapies.<sup>6</sup> The role of radiotherapy remains questionable.

Recently, Rhee et al reported a 7-year-old female with bladder ASPS as a second primary malignancy.<sup>3</sup> The patient received chemotherapy (vincristine, cyclophosphamide, cisplatin, carboplatin) and (nonpelvic) radiation for retinoblastoma during infancy. Previously, an 18-year-old adult male developed bladder ASPS as a secondary malignancy after receiving chemotherapy and pelvic radiation for testicular relapse of acute lymphoblastic leukemia.<sup>9</sup> Tanabe et al recently described the first case of primary pediatric bladder ASPS in a 9-year-old female, who was treated with cystourethrectomy and urinary diversion.<sup>2</sup> Our patient represents the second pediatric case of ASPS as a secondary malignancy after chemotherapy without prior pelvic radiation.

Exposure to DNA disrupting agents in this patient may have led to development of ASPS via induced chromosomal translocation. The ASPSCR1-TFE3 translocation that characterizes ASPS is identical to that of Xp11 translocation-associated pediatric RCCs, which is a relatively common secondary malignancy in neuroblastoma patients.<sup>4,16,17</sup> Work by Argani et al in translocation based pediatric RCC reveal 15% of patients with chromosomal translocations (including ASPSCR1-TFE3) received prior treatment with cyclophosphamide, etoposide, or doxorubicin.<sup>18</sup> Although rare, Xp11 translocation-associated RCC has been described in neuroblastoma patients after chemotherapy.<sup>16,17</sup> Cyclophosphamide and other cytotoxic agents have been clearly demonstrated to increase the risk of secondary malignancies including leukemias, soft tissue sarcomas, and malignant gliomas.<sup>18-20</sup>

Our patient was interestingly found to harbor a variant of unknown significance in the PTCH1 gene (9q22.32), commonly associated with nevoid basal cell carcinoma syndrome, known to increase the risk of basal cell carcinoma and medulloblastoma. Her genetic variant was thought unlikely related to development of her 2 primary malignancies.

We pursued open cystotomy and tumor excision, felt easily performed by excising the mass off its thin stalk for diagnostic purposes, then later partial cystectomy and lymphadenectomy for definitive resection. An argument can be made for initial transurethral resection for diagnosis, however the risk of nondiagnostic biopsy was considered, and this was actually demonstrated by Rhee et al. To date, treatment of bladder ASPS has been variable, from complete transurethral resection to cystourethrectomy and urinary diversion.<sup>2,3</sup> In this case, partial cystectomy was performed, achieving negative margins and leaving adequate bladder capacity to maintain normal voiding while also providing valuable whole-tissue and lymph node sampling to stage the disease, which is not achieved with transurethral resection. Further follow-up is necessary for all pediatric bladder ASPS cases to determine if surgical choice impacts recurrence or survival.

## CONCLUSION

To our knowledge, this is the seventh reported case of bladder ASPS, the third pediatric case, and the second pediatric case as a secondary malignancy after chemotherapy. This report adds to the ASPS body of knowledge and should serve to highlight the vigilance required in surveilling pediatric patients who receive cytotoxic chemotherapies, as the possibility of developing secondary neoplasms is clearly demonstrated.

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