Synchronous, but separate, bladder and vaginal rhabdomyosarcoma: a novel genetic case report

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Embryonal rhabdomyosarcoma is a rare cancer that often requires multimodality therapy to treat; however, these therapies can cause changes in the biology of the tumor. Several reports have documented pathologic changes but only recently have genetic changes been mapped. We present case of two separate synchronous primary rhabdomyosarcomas in a 17-month-old patient and discuss the pathophysiology and genetic changes that occur with treatment. We hypothesize that a genetic field defect arising in development of the urogenital sinus caused the tumors, but that treatment modalities may have caused genetic alterations changing clinical behavior of the tumors and responses to treatment.

Key Words: pediatric urology, rhabdomyosarcoma, genetics, cystectomy, vaginectomy

Introduction

Embryonal rhabdomyosarcoma is a rare cancer that can arise as early as 6-8 weeks of embryonic development from skeletal muscle precursor cells and is most common among males. This type of sarcoma can therefore be found in various parts of the body concurrently rather then as a result of a metastasis to another organ. There is literature suggesting a genetic variable may be involved in its pathogenesis; however, the cause is unknown in the majority of incidents of rhabdomyosarcoma. It has been found that multimodal treatment results in high 5 year survival rates with classic embryonal having a 92% 10 year survival rate.[1]

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We present a patient who was diagnosed with the most common rhabdomyosarcoma (embryonal, botyroid) of both the bladder and the vagina that were anatomically and genetically distinct. With genetics playing a larger role in treatment selection, it is important to understand genetic pathophysiology as different modalities can alter the behavior of the tumor. Our patient's treatment included chemotherapy, radiation, and surgery to remove the masses and affected areas in order to attempt salvage functional outcomes. We focus our report on the clinical pathway of the patient with a discussion of the genetic alterations.

Case report

A 17 month previously healthy female presented to the emergency department with vaginal bleeding and was discharged with "urethral prolapse" and treated with topical steroids. The prolapse worsened over the next month and dedicated imaging demonstrated a 4.1 cm x 3.8 cm vaginal mass and several bladder masses, Figure 1a. Endoscopic biopsies from both the bladder

and vagina returned embryonal rhabdomyosarcoma, botryoid variant, in both locations. Complete metastatic evaluation showed only localized disease. Due to the tumor burden, she underwent 40 weeks of chemotherapy (Vincristine, Dactinomycin, Cyclophosphamide, Irinotecan) and 6 weeks of pelvic radiation following laparoscopic ovariopexy. Imaging upon completing medical therapy demonstrated near resolution of the vaginal mass and improvement of the bladder masses, Figure 1b.

Two months later, the patient had rapidly progressing pain with defecation and increased vaginal bleeding. Physical examination demonstrated progression of disease with tissue protruding from the urethra and her serum creatinine rose from 0.2 mg/dL to 2.9 mg/dL, Figure 2. MRI demonstrated a 6.2 cm x 4.8 cm bladder mass protruding into the urethra and bilateral hydronephrosis, Figure 1c. Bilateral nephrostomy tubes were placed with normalization of renal function. Due to the tumor's rapid growth and prior chemotherapy and radiation, tumor board agreement was for cystectomy, partial distal vaginectomy and bilateral ureterostomies.

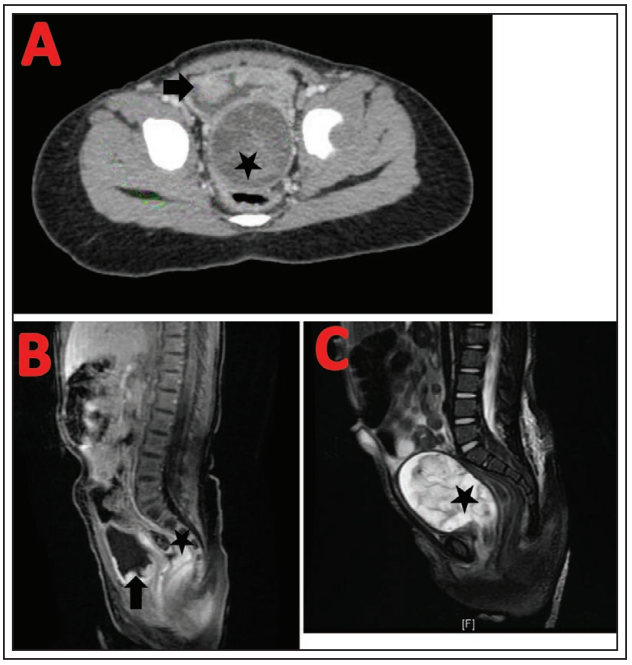

Figure 1. A) Initial CT demonstrating vaginal (black star) and bladder masses (black arrow). **B)** Interval MRI after completion of chemotherapy and radiation demonstrating nearly complete resolution of the vaginal mass (black star) and bladder tumors (black arrow). **C)** Follow up MRI of radidly exanding bladder mass (black star). Note the almost complete resolution of the vaginal mass.

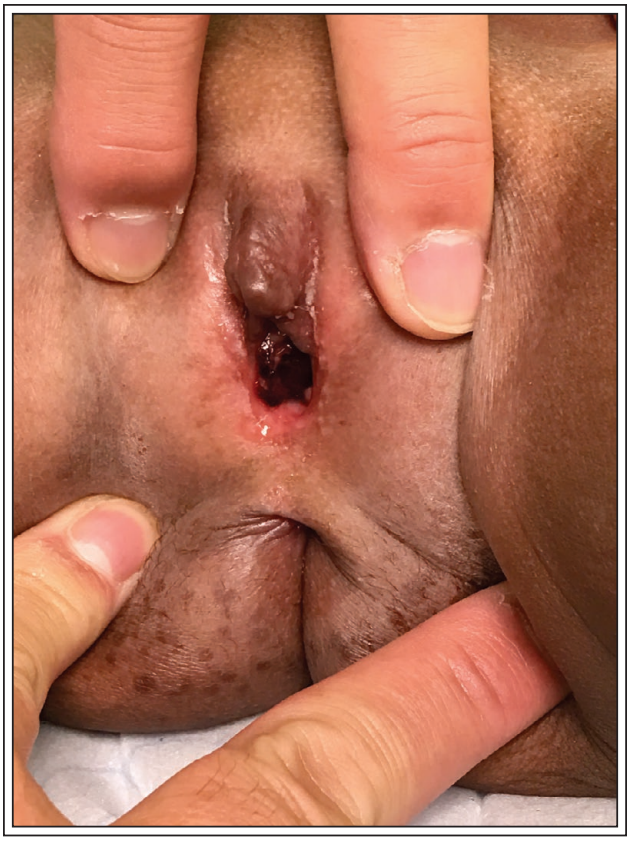

Figure 2. Physical exam demstrating botryoides prolasping from the patient urethra.

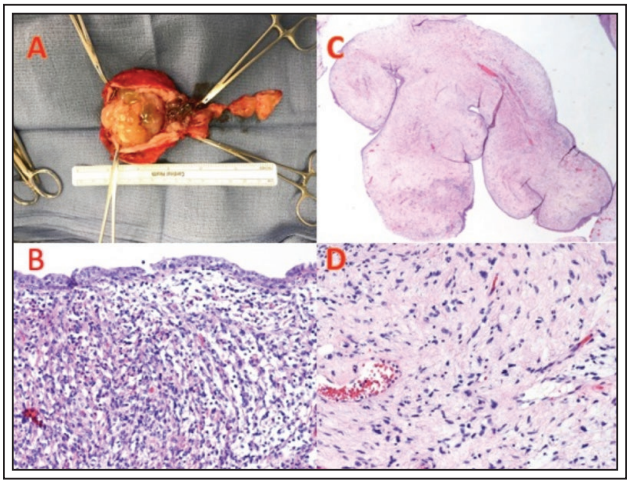

Figure 3. A) Bladder with tumor, macroscopic. **B)** Bladder neoplasm, intermediate magnification, H&E. Cellular blue cell neoplasm with cytodifferentation. **C)** Vaginal mass, low magnification, H&E. **D)** Vaginal mass, higher magnification, H&E. Atypical stromal cells at margin.

Pathology, Figure 3, demonstrated a bladder filled by a pedunculated tumor resembling a cluster of grapes. Histologic examination revealed an embryonal rhabdomyosarcoma with botyroid morphology confined to the superficial muscularis propria. The vaginal wall tissue contained variable amounts of embryonal rhabdomyosarcoma with botryoid morphology, confined to the mucosa. The bladder and vaginal tumors had no evidence of connection between the two tumor sites. In the original resection of the vaginal mass the NRAS – Q61K mutation was found, but at the time of vaginectomy a new subclonal variant of the Q61K mutation (G60R) was identified in the same mass, and a new mutation was found in the ZRSR2 (R448_R449insSRSR) gene, as well. At the time of the cystectomy and vaginectomy, the bladder also contained the ZRSR2 mutation and, in addition had two separate mutations, MYC amplification and TP53 (A189D). None of these mutations currently have FDA-approved chemotherapy treatments.

Follow up imaging 11 months post-surgery revealed no evidence of recurrent or residual tumor.

Discussion

Rhabdomyoscarcoma is the most common pediatric soft tissue malignancy. Tumors arising from the bladder and/or prostate have a worse 5 year survival rate than paratesticular, vaginal or ureterine tumors, 70% to 73% verses 84% to 89%, respectively.[1,2] However, this patient is unique as it appears she had two separate primary tumors as evidenced by both the varying response to medical therapy as well as the pathologic and genetic findings. Q61K is a missense mutation that encourages cell proliferation. G60R is another missense mutation, but its effect on the NRAS protein function remains unclear. The TP53 gene identified from the bladder mass codes for a protein that acts as a transcription factor and serves as a key regulator of the cell cycle. The inactivation of p53 disrupts the cell cycle and may lead to tumor formation. Tumors with intact TP53 respond well to chemotherapy and/or radiation treatment. ZRSR2 also found in the bladder mass resection is involved in the selection of splice sites of introns. Mutations in these genes most likely reflect defects as recognition during RNA splicing. The mechanism through which the splicing factor mutations misregulate RNA splicing and subsequently lead to disease is still unknown. None of these mutations currently have FDA-approved chemotherapy options available for these affected organs.

Recent investigations have identified genetic translocations found in patients with rhabdomyoscarcoma that alter patient's prognosis depending on the subtype. In particular, the alveolar subtype there have been translocations t(1;13)/PAX7-FKHR and t(2;13)/PAX3-FKHR leading to worse prognosis in 80% of this subtype; also, other genetic mutations have been found in genes in bladder rhabdomyosarcoma.[3-5] In addition, Leuschner et al has noted high occurrence of maturated tumor cells in patients with local recurrence postchemotherapy.[1] With these genetic and histological findings in mind, we hypothesize a possible field genetic defect arising from the urogenital sinus giving rise to two separate but simultaneous tumors. The original chemotherapy and radiation treatment may have caused further mutation and maturation of Q61K and ZRSR2 genes and noting changes in the genetics of the tumor may lead to future new chemotherapy options.

Conclusion

We present a unique case of two separate primary rhabdomyosarcomas in a 17-month-old patient that is hypothesized to have a genetic field defect arising in development of the urogenital sinus. Children who present with urogenital symptoms require immediate evaluation for rhabdomyosarcoma due to its rapid tumor cell growth and complications. This patient was treated with chemotherapy followed by radiation; however, due to the aggressive nature of these tumor cells, a cystectomy, and partial distal vaginectomy to help alleviate further tumor growth. Follow up imaging determined that treatment resulted in no evidence of disease, but the genetic changes within the tumor and the pathologic changes are important to understand for therapeutic purposes. Future studies of genetic tumor evaluation and embryonic development studies are required to understand the early cell mutation and maturation of these tumors and thus may lead to new chemotherapy targets. □

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