Leiomyosarcoma of the bladder in a 16-year-old girl with a history of cyclophosphamide therapy for bilateral retinoblastoma during infancy

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ABSTRACT

A 16-year-old female with bladder leiomyosarcoma had a history of bilateral retinoblastoma at 6 months of life. She received cyclophosphamide chemotherapy after surgical enucleation. In this report, we discussed the possible role of retinoblastoma or cyclophosphamide as a target for the development of bladder leiomyosarcoma.

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Second tumors are known to develop at remote sites in survivors of hereditary or childhood retinoblastoma, and are characterized by having a cumulative incidence with aging.[1] Among these tumors is leiomyosarcoma of the bladder which constitutes about 0.5% of bladder tumors.[2] To our knowledge, there are very few reports on leiomyosarcoma of the bladder with a history of retinoblastoma associated with cyclophosphamide treatment.[3-5] We present a new case with a history of bilateral retinoblastoma during infancy that was treated by enucleation followed by cyclophosphamide therapy.

Case Report. A 16-year-old Saudi girl presented with painless hematuria and frequency of micturition for 5 months. The girl had enucleation of both eyes for bilateral retinoblastoma at the age of 6 months, and received cyclophosphamide as well as radiotherapy and vincristine for one year postoperatively. Her examination revealed no any palpable masses, organomegaly or lymphadenopathy. Her liver and kidney functions were within normal ranges. There were no malignant or atypical cells in the urine cytology. Intravenous urography showed a large irregular-filling defect that filled most of the bladder cavity. Pelvic ultrasound showed a large mass that was heterogeneous in echogenicity. It filled most of the bladder cavity. In unenhanced CT, the mass was 100 Hounsfield (HUs) units in density and arising from the anterior wall with a sessile stalk. The computerized tomography scan (**Figure 1**) revealed no evidence of lymphadenopathy or metastasis. Cystoscopic examination revealed a large well-circumscribed sessile mass in the anterior wall. The mass had a smooth surface, and was largely covered by intact mucosa. Multiple cup biopsies showed an infiltrating neoplasm composed of relatively uniform interlacing fascicles of spindle-shaped cellular growth. The nuclei were large, pleomorphic, hyperchromatic and cigar shaped. There was 15-20 mitotic activity per high power field. The cytoplasm was abundant and eosinophilic (**Figure 2**). Immunohistochemical staining was positive for the mesenchymal immunoreactive stains vimentin, desmin and smooth

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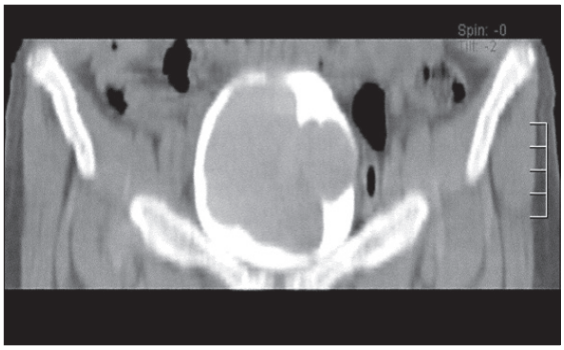

Figure 1 - Coronal CT images showing 100 Hounsfield units density mass, arising from the anterior wall with a sessile stalk.

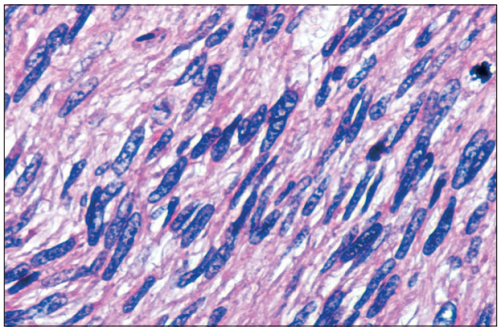

Figure 2 - Hematoxylin and Eosin stain showing spindle cell cellular growth. Mitotic activity is obvious. The nuclei are pleomorphic, hyperchromatic and cigar shaped.

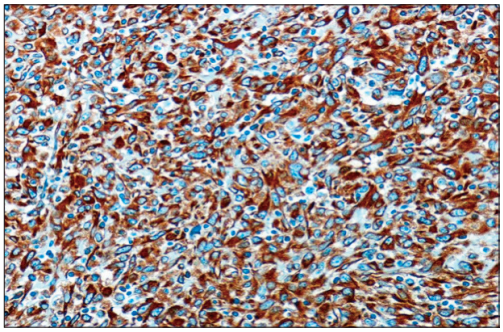

Figure 3 - Diffusely and strongly positive vimentin stain.

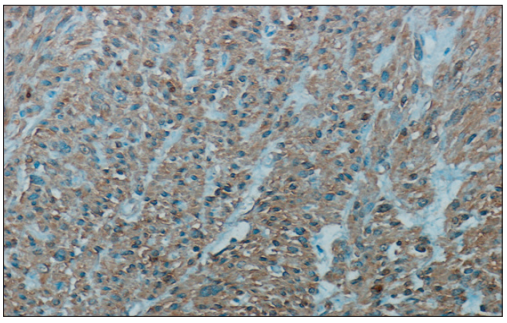

Figure 4 - Positive smooth muscle actin stain.

muscle actin, but was negative for the epithelial immunoreactive stain cytokeratin (**Figures 3 & 4**). Final diagnosis was a highly malignant spindle cell tumor that was consistent with leiomyosarcoma of the urinary bladder. Cystectomy was carried out, and the patient was referred for postoperative radiotherapy.

Discussion. Non-ocular primary tumors, especially osteosarcoma, are known to develop in survivors of hereditary retinoblastoma.[3] Few reports suggested that cyclophosphamide treatment in patients with a history of retinoblastoma can target the development of leiomyosarcoma of the bladder as a second tumor.[4,5] However, bladder leiomyosarcoma develops after cyclophosphamide treatment for malignancies other than retinoblastoma.[6-8] It also develops after retinoblastoma without cyclophosphamide treatment.[2] Both hereditary retinoblastoma and cyclophosphamide treatment were found to stimulate development of second tumors through gene mutation. Hereditary retinoblastoma causes stimulation of the second retinoblastoma gene (RBl) allele,[10] whereas, the metabolites of cyclophosphamide, especially acrolein, that are excreted in urine cause acute toxicity to the bladder mucosa and possibly hemorrhagic cystitis. This is followed by rapid epithelial regeneration and increased risk of mutation.[4] Patients who were previously exposed to cyclophosphamide therapy will have a higher incidence of developing leiomyosarcoma of the urinary bladder than the general population; 9.2% and 0.5% successively.[9] The relative risk of developing bladder cancer was increased up to 6.4 fold in cyclophosphamide-exposed patients. The risk increases up to 11.3 when hemorrhagic cystitis is present.[4] It is suggested from these findings that the risk of development of leiomyosarcoma of the bladder is increased in the presence of a history of hereditary retinoblastoma or cyclophosphamide treatment. This risk is further accentuated in the presence of a history of hereditary retinoblastoma followed by cyclophosphamide treatment.

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