A High-Grade Primary Leiomyosarcoma of the Bladder in a Survivor of Retinoblastoma

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- Second nonocular malignancies develop with increased incidence in patients with hereditary retinoblastoma. Osteosarcoma is by far the most common type with an incidence of up to 50%, followed by soft tissue sarcomas. Visceral leiomyosarcoma is extremely rare and only 2 cases have been reported in the past 2 decades, one in the liver and another one in the urinary bladder, both of which developed after cyclophosphamide therapy. Here we report a case of vesical leiomyosarcoma that was diagnosed in a 49-year-old woman 47 years after the diagnosis of a hereditary retinoblastoma. The patient's retinoblastoma was treated with unilateral enucleation without adjuvant radiation or chemotherapy. We believe that this is the first report of vesical leiomyosarcoma occurring in a patient with retinoblastoma without a prior history of radiation or chemotherapy. This report is significant not only because of the rarity of vesical leiomyosarcoma as a second nonocular tumor in retinoblastoma patients, but also because of the infrequency of vesical leiomyosarcoma in general. We also investigated the potential molecular pathogenesis of the leiomyosarcoma.

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Retinoblastoma is a rare childhood tumor with an incidence of 1 per 20,000 live births. It may be familial or sporadic in origin. Familial cases show an autosomal dominant inheritance pattern and are usually bilateral and multifocal. The majority of retinoblastomas, however, are sporadic and are almost exclusively unilateral and unifocal. The occurrence of the tumor, in its familial and sporadic form, is attributable to mutation of the Rb1 gene located at chromosome 13q14.2 Study of the Rb1 gene shows mutation at both alleles. The familial form is associated with a germ line mutation of Rb1. During the development of the retinoblastoma, a second somatic mutation occurs. In the sporadic form, both copies of Rb1 undergo somatic mutation.

The propensity for survivors of heritable retinoblastoma to develop second nonocular malignancies is well known. It was initially reported that second tumors occur within the field of irradiation. Subsequently, it was demonstrated that second tumors could also develop outside the field of radiation or after chemotherapy. The major controversy, however, is the actual magnitude of the risk of second tumors among survivors of retinoblastoma. Over a variety of second tumors have been reported.6 Osteosarcoma is most commonly reported, with an incidence of up to 50%. Fibrosarcomas account for about 20%. Leiomyosarcomas have rarely been reported. They have been described in soft tissues adjacent to the orbit, femur, and maxilla. Only 2 visceral leiomyosarcomas have been described, one each in the liver and bladder.6 The leiomyosarcomas occurred in patients with history of radiation and/or chemotherapy as primary or adjuvant therapy for their retinoblastoma. However, there have been no reported cases of leiomyosarcoma of the urinary bladder in a survivor of retinoblastoma who had no history of radiation or chemotherapy. We report the case of a 49-year-old woman with a family history of retinoblastoma who developed a unilateral retinoblastoma at age 2 and was treated with enucleation, without adjuvant radiation or chemotherapy. We believe that this is the first occurrence of a visceral leiomyosarcoma in a patient with retinoblastoma treated without any adjuvant therapy and is only the second case of a bladder leiomyosarcoma reported in a patient with retinoblastoma.

REPORT OF A CASE

A 49-year-old woman presented with a 1-week history of left flank pain and hematuria. Initial evaluation with a non–contrast-enhanced abdominal computed tomography scan showed a stone measuring 2 to 3 mm in diameter in the central portion of the left kidney and a second stone at the left ureterovesical junction. Over the next few days, the woman passed a stone and improved with oral pain medication. Two to 3 weeks later, gross hematuria recurred, with clots, and the patient suffered an episode of syncope because of a low hematocrit (0.20 [20%]). Repeated abdominal computed tomography scan with contrast enhancement revealed a large filling defect in the lumen of the bladder (Figure 1, arrowhead). A large pedunculated bladder tumor arising from the left side of the bladder near the dome was seen on flexible cystoscopy. A biopsy of the tumor revealed a high-grade leiomyosarcoma. The patient's past history revealed that she had developed a unilateral retinoblastoma that was treated with enucleation without adjuvant therapy at age 2. Her family history was significant for retinoblastoma in one sibling.

The results of a bone scan for metastases were negative. The patient then underwent anterior exenteration (radical cystectomy, hysterectomy, and bilateral salpingo-oophorectomy) and ileal loop urinary diversion. She was followed postoperatively without any adjuvant therapy. Unfortunately, 18 months after the initial diagnosis of leiomyosarcoma of the bladder, she developed mul-
A resection specimen from the radical cystectomy, hysterectomy, and bilateral salpingo-oophorectomy was received in the Pathology Department. The lumen of the bladder was inflated with 10% buffered formalin, and the entire specimen was fixed before dissection. Tissue sections were embedded in paraffin and stained with hematoxylin-eosin. For immunohistochemical staining, formalin-fixed, paraffin-embedded tissue sections were cut at 5 μm and treated with 0.1 mol/L citrate, pH 6.0, in an 800-W microwave oven for 15 minutes for antigen retrieval before immunostaining. Primary antibodies to pRb (Dako, Carpinteria, CA), p53 (Oncogene Research Products, Cambridge, Mass: a mixture of Ab-2 and Ab-6), cyclin D1 (Novocastra Laboratories Ltd, Newcastle upon Tyne, UK), smooth muscle actin, and desmin (Dako) were used. Immunostaining was done with the avidin-biotin-peroxidase kit (Ventana Medical Systems, Tucson, Ariz), p53 (Oncogene Research Products, Cambridge, Mass: a mixture of Ab-2 and Ab-6), cyclin D1 (Novocastra Laboratories Ltd, Newcastle upon Tyne, UK), smooth muscle actin, and desmin (Dako) were used. Immunostaining was done with the avidin-biotin-peroxidase kit (Ventana Medical Systems, Tucson, Ariz), according to the manufacturer’s specifications. The slides were counterstained with hematoxylin. The negative controls were the same tissue sections processed identically for immunostaining process except for the omission of the primary antibody. The positive controls for p53 and pRb were a cancer and a normal epithelium that were known to contain a p53 mutation and normal pRb, respectively.

Immunoreactivity for p53 and pRb was determined by positive nuclear staining. The final evaluation of staining was based on published criteria. For p53, negative staining was defined as an absence of staining in all nuclei. For pRb, normal staining was defined as staining of neoplastic nuclei throughout the tumor, whereas abnormal staining was defined as absent staining or staining in a scattered, or focal distribution in the tumor. The staining was defined as inconclusive if both neoplastic and normal urothelial nuclei did not stain or stained only weakly.

RESULTS

Gross Description

The resection specimen consisted of a bladder, a uterus with cervix, bilateral ovaries, and bilateral fallopian tubes. A tan-yellow firm mass measuring 9.0 × 6.5 × 6.0 cm was present in the left lower anterior wall of the bladder, near the dome. The tumor was exophytic, polyloid, and pedunculated, with a 1.5-cm stalk. The cut surface of the tumor was tan-white and fleshy with a whorled appearance. Foci of hemorrhage and necrosis were present. The bladder mucosa was unremarkable.

Dissection of the uterus, cervix, ovaries, and fallopian tubes showed multiple well-circumscribed, tan-pink, firm leiomyomas in the myometrium, ranging in size from 0.7 cm to 2.0 cm in greatest dimension. The remaining uterus, cervix, ovaries, and fallopian tubes were otherwise unremarkable.

Microscopic Description

Sections of the bladder showed that the tumor originated in the muscularis propria and penetrated the bladder wall in the area of the stalk. The tumor exhibited a fascicular growth pattern (Figure 2, A). The tumor cells had elongated blunt-ended nuclei and acidophilic fibrillar cytoplasm. There was marked nuclear pleomorphism with atypia (Figure 2, B) and a high mitotic rate (more than 22 mitotic figures per 10 high-power field). Focal necrosis was present, and vascular invasion was not seen. Immunohistochemical studies showed that the cells expressed the smooth muscle actin (Figure 2, C) and desmin (data not shown) characteristic of leiomyosarcoma. Most of tumor cells were negative for pRb with scattered weak nuclear staining (Figure 2, D). Overlying normal urothelial cells were positive for pRb (Figure 2, D, insert). The results of staining for p53 and cyclin D1 were negative (data not shown).

No tumor was detected in the right and left obturator lymph nodes. Only leiomyoma was found in the myometrium of the uterus. No atypia or mitosis was noted.
Figure 2. Microscopic findings of the vesical tumor. A, Low-power view of the tumor consisting of fascicles of spindle cells arranged in interlacing bundles. Normal urothelium is shown in the left lower corner (hematoxylin-eosin, original magnification ×100). B, High-power view of the tumor cells showing marked pleomorphism with atypia and many mitotic figures (arrowheads) (hematoxylin-eosin, original magnification ×400). C and D, Immunohistochemical staining of tumor cells that are positive for smooth muscle actin (C) and negative for pRb (D) (immunoperoxidase, original magnification ×200). Insert in panel D shows nuclear staining for pRb in the overlying normal urothelial cells; this staining was used as an internal positive control (original magnification ×200).

ported in a patient with retinoblastoma who had no history of radiation or chemotherapy. The latency of the onset of the tumor was 47 years. Although the patient had unilateral retinoblastoma, her positive family history makes it highly unlikely that she had sporadic retinoblastoma.

It is not likely that the leiomyosarcoma of the bladder was secondary to a metastasis from a uterine leiomyoma because the uterine tumor was very small and had a bland microscopic appearance and a lack of necrosis and mitosis, whereas the vesical tumor was a large, high-grade lesion with marked pleomorphism and necrosis and numerous mitotic figures.

There is limited information about the molecular pathogenesis of leiomyosarcoma. Several reports have demonstrated abnormalities in the p53 pathway as well as in the Rb-cyclin D pathway in leiomyosarcoma.9,10

The p53 gene is a tumor suppressor gene encoding a 53-kd nuclear phosphoprotein. The phosphoprotein acts as a transcription factor; recognizes specific DNA sequences located adjacent to several different genes; and is intimately involved in the regulation of transcription, DNA repair, and apoptosis. Mutation of p53 leads to accumulation of an abnormal p53 protein that is more resistant to degradation than the wild type protein. Several reports in recent years have described alterations in the p53 gene and/or protein in about 20% of leiomyosarcoma of soft tissue origins.9 However, analysis of p53 protein demonstrated no abnormality in our case, suggesting that the p53 pathway is not a preferred target for molecular abnormalities.

The Rb gene is a tumor suppressor gene encoding a 110-kd nuclear phosphoprotein. It is involved in cell cycle control, as it prevents the cell from entering the S phase of the cell cycle by sequestering the E2F family of transcription factors. The phosphorylation of pRb by the cyclin-cyclin-dependent kinase complex relieves the block on E2F proteins, which are then able to transactivate those genes involved in DNA replication. Recently, p16, the product of the CDKN2/MTS1 gene, has been shown to inhibit the cyclin-dependent kinase complex, thereby mimicking the tumor-suppressing function of pRb. Abnormalities in the p16-cyclin D-Rb pathway, including mutations and deletions of the genes, are very common in human carcinomas12 and sarcomas.10 In one study, as many as 90% of leiomyosarcoma had abnormalities of pRb and p16 expression.10 In our study, expression of pRb was aberrant in leiomyosarcoma cells but normal in the overlying urothelial cells. This finding is similar to that of Cohen et al.10 Unfortunately, assessment of p16 status in our case...
was not possible because of a lack of antibody resources for paraffin-embedded tissue sections.

In summary, we have reported a case of primary vesical leiomyosarcoma in a 49-year-old woman with a history of hereditary retinoblastoma. This report illustrates that a prior history of radiation or chemotherapy is not always an identifiable contributing factor in the development of rare visceral leiomyosarcomas as second malignancies in patients with hereditary retinoblastoma. Loss of pRb expression may have played an important role in the pathogenesis of this case.

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References