CASE REPORT

Soft tissue, pelvic, and urinary bladder leiomyosarcoma as second neoplasm following hereditary retinoblastoma

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There is an increased incidence of second primary tumours in survivors of hereditary or childhood retinoblastoma. The cumulative incidence varies widely in different long term follow up series, from 8.4% at 18 years to 90% at 30 years. Second malignancies may arise at a site of previous radiotherapy or distantly. Histological subtypes of second malignancies include osteosarcoma, pincaloblakoma (these are now considered trilateral retinoblastomas), malignant melanoma, a variety of soft tissue sarcomas, and epithelial malignancies. Most soft tissue tumours are osteosarcomas. Leiomyosarcomas are comparatively rare with, as far as we are aware, only 18 reported cases. Second primary tumours may be classified into malignant or benign, and can occur in any site.
Histology showed a cellular lesion composed of plump spindle shaped cells with abundant eosinophilic cytoplasm (fig 5). Tumour cell nuclei were moderately pleomorphic and the mitotic count was 8/10 high power fields. Foci of necrosis were present. The tumour exhibited widespread positivity for α smooth muscle actin and desmin. MIB1 staining showed a proliferation index of 40%. Staining for cyclin D1 was negative, whereas most tumour cell nuclei were positive for p53 (fig 6). The tumour was interpreted as an intermediate grade leiomyosarcoma.

DISCUSSION

Long term survivors of hereditary retinoblastoma are at risk of developing a variety of non-ocular second primary malignancies, the most common histological subtype of which is osteosarcoma. The reported risk varies widely, but a cumulative incidence of 1% for each year of life has been suggested as an approximate estimate. Earlier reports indicated that many of these malignancies are radiation or chemotherapy induced. However, more recent studies suggest that the development of second primary neoplasms in patients with hereditary retinoblastoma results partly from a genetic predisposition and partly from the potentiating effect of
radiotherapy on tumorigenesis through mutation of the second retinoblastoma gene (RB1) allele, the first RB1 allele being mutated in all patients with hereditary retinoblastoma.\textsuperscript{20}

Leiomyosarcomas are relatively rare neoplasms outside the uterus and the gastrointestinal tract. Retroperitoneal leiomyosarcomas form the largest group of soft tissue leiomyosarcomas.\textsuperscript{21} In retinoblastoma survivors, some of the reported leiomyosarcomas have been in the field of radiation,\textsuperscript{9–11} whereas others have been described at distant sites, such as the urinary bladder, liver, and femur.\textsuperscript{9–12} One urinary bladder leiomyosarcoma developed 14 years after chemotherapy with cyclophosphamide for retinoblastoma.\textsuperscript{22} There was no history of chemotherapy in the two cases we describe. In female patients, uterine leiomyosarcoma has not been reported after hereditary retinoblastoma, although simultaneously occurring benign uterine leiomyomas have been described.\textsuperscript{3} One of the patients we describe also had uterine leiomyomas. We feel this is a coincidental association, although it is possible that, because of genetic factors, there is an increased risk of the development of smooth muscle neoplasms at various sites.

“The RB gene is a tumor suppressor gene encoding a nuclear phosphoprotein that functions as a regulator of cell cycle progression”

A recent analysis of second primary neoplasms in retinoblastoma survivors revealed that 76% of the second tumours occurred in the head and neck region and that soft tissue sarcomas were the single largest category, comprising 24% of the total.\textsuperscript{3} The median age at diagnosis of second tumour for the entire series was 16.4 years. The youngest patient to develop a soft tissue tumour was 4 years old and the oldest was 41. Previously reported cases of leiomyosarcoma occurring outside the head and neck region have been in the 4th to 6th decades. The cases we report, together with others described, suggest that with increasing duration of survival after hereditary retinoblastoma there is an increased risk of developing leiomyosarcoma in areas remote from the site of irradiation. Such patients thus require appropriate follow up.

The patient in case 1 developed a leiomyosarcoma of the pelvic soft tissues 18 months after removal of the leiomyosarcoma from the thigh. It is probable that the pelvic leiomyosarcoma was a metastasis from the thigh neoplasm, although we cannot exclude the possibility of synchronous development of independent leiomyosarcomas. We could not demonstrate the expression of cyclin D1 immunohistochemically in either of the leiomyosarcomas. One tumour was negative for p53 but the other exhibited diffuse nuclear positivity. The RB gene is a tumour suppressor gene encoding a nuclear phosphoprotein that functions as a regulator of cell cycle progression. This function is lost when the protein is phosphorylated by cyclin dependent kinases. p16, a product of the CDKN2/MTS1 gene, is known to inhibit phosphorylation by cyclin dependent kinases in a manner similar to the retinoblastoma protein. p53 and retinoblastoma protein-cyclin D pathway abnormalities have been detected in sporadic leiomyosarcomas in recent studies.\textsuperscript{22, 23}

In summary, we report two cases of leiomyosarcoma developing 36 and 38 years after bilateral hereditary retinoblastoma. In both cases, the leiomyosarcoma occurred outside the head and neck region. Patients with hereditary retinoblastoma are probably at increased risk of developing leiomyosarcoma and other soft tissue sarcomas with the increasing duration of survival.

**Take home messages**

- We report two patients who developed leiomyosarcoma, outside the head and neck region, following hereditary retinoblastoma 36 and 38 years earlier.
- In survivors of hereditary retinoblastoma there is an increased risk of the development of sarcoma, most commonly osteosarcoma, especially with the increasing duration of survival.
- Leiomyosarcomas developing as a second malignancy have rarely been reported and most have occurred in the field of previous radiotherapy.

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