Quadruple Neoplasms following Radiation Therapy for Congenital Bilateral Retinoblastoma

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Established Facts

- Patients with hereditary retinoblastoma treated by radiation are susceptible to the development of secondary neoplasms.

Novel Insights

- Radiation can induce multiple tumors, in this case 4, and long-term follow-up surveillance is essential in hereditary retinoblastoma patients treated with radiation.

Keywords

Bilateral retinoblastoma · Postradiation neoplasm · Undifferentiated pleomorphic sarcoma · Schwannoma · Radiation-induced meningioma

Abstract

Purpose: The aim of this study was to describe a 34-year-old male with hereditary bilateral retinoblastoma treated with radiotherapy as a child who developed 4 distinct tumors within the radiation field. **Methods:** A 34-year-old male with bilateral retinoblastoma status postradiation therapy and recurrence requiring enucleation presented with left-eye visual acuity changes. Magnetic resonance imaging demon-

strated a left orbital mass and a right parasellar complex lobulated mass (right sphenoid and right cavernous sinus). Two weeks later, the patient underwent excision of the orbital mass and biopsy of an upper-lid nodule. This was followed by craniotomy for removal of the complex mass. **Results:** Histology revealed 4 distinct tumors, including an undifferentiated pleomorphic sarcoma (left orbit), a radiation-induced meningioma (right sphenoid), a schwannoma (right cavernous sinus), and a basal-cell carcinoma (left lid). **Conclusion:** Although occurrence of a second neoplasm is a well-known outcome following radiation treatment in patients with hereditary retinoblastoma, the diagnosis of 4 additional neoplasms is rare. Pleomorphic sarcoma, radiation-induced meningioma, and schwannoma are uncommon tu-

mors and not well represented in the literature describing irradiated retinoblastoma patients. Secondary malignancies are a leading cause of early death in retinoblastoma survivors, and long-term follow-up is crucial for patient care.

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Introduction

Retinoblastoma is a primitive tumor that arises from immature cells of the retina and is the leading intraocular malignancy in the pediatric population. In addition to the globe, retinoblastoma may also originate along midline intracranial locations such as pineal and sellar/suprasellar regions. Each year, approximately 300 children and adolescents are diagnosed with retinoblastoma in the United States. Two-thirds of these cases occur in children younger than 2 years of age, and approximately 95% of the cases occur before the age of 5 years [1]. The genetic basis of retinoblastoma lies in mutations causing inactivation of both alleles of the tumor suppressor gene *RB1*, located on the long arm of chromosome 13 at the small region of q14 [2]. The *RB1* gene is critical in controlling cell-cycle progression, and abnormalities of this gene have been found to occur in many types of cancer [3, 4].

Retinoblastoma is classified into heritable (25–30%) and nonheritable forms (70–75%). Heritable forms indicate a germline mutation in the *RB1* gene. Patients with heritable retinoblastoma are diagnosed by the presence of bilateral disease, a family history of retinoblastoma, or molecular detection of a pathogenic variant in the *RB1* gene. In contrast, the nonheritable form is usually unilateral, unifocal, and stems from somatic mutation of the *RB1* gene. Children with germline mutations present at an earlier age (12 months) compared to children with the nonheritable forms of retinoblastoma (23 months).

A variety of treatment modalities, including different modes of radiation therapy, chemotherapy regimens, intraocular laser coagulation and cryocoagulation, have led to high rates of survival for retinoblastoma patients, with an average 5-year survival of 93% [5]. Patients with heritable forms have an increased lifelong risk of developing secondary neoplasms, both within and outside of the field of radiation [6]. In contrast, patients with nonheritable forms have a risk for developing subsequent cancers equivalent to that of the general population, even when treated with radiation. We present a case of a patient with bilateral retinoblastoma who developed 4 distinct tumors all occurring within the radiation field 33 years after radiation therapy.

Case Presentation

A 34-year-old male with a childhood history of bilateral retinoblastoma treated with bilateral orbital cobalt irradiation in England and recurrence of right-eye retinoblastoma requiring enucleation, who was not undergoing any routine surveillance studies or imaging, presented to a tertiary care center for evaluation of vision changes in his left eye. He was not undergoing any routine surveillance studies or imaging. The patient complained of mild constant pain with decreased acuity that had become progressively worse. On examination, visual acuity was found to be 20/200 in his left eye. Intraocular pressure of the left eye was 21 mm Hg by tonopen. His left pupil was reactive, extraocular movements were full, and alignment was orthotropic. The anophthalmic socket was examined and was negative for any significant abnormalities. Lid examination showed a nodule near the left upper-lid margin. On slit-lamp examination, a superomedial orbital mass was noted. Magnetic resonance imaging of the orbit demonstrated a 2.8 (sagittal) × 2.2 (anterior-posterior) × 1.7 (transverse) cm mass medial to the globe. The mass displaced the globe anteriorly and laterally. The mass did not show radiologic evidence of invasion into the globe or involvement of extraocular muscles or bone. Moreover, an additional complex 5.4-cm lobulated mass was seen involving the right parasellar region, including the right sphenoid wing and the right cavernous sinus (Fig. 1a).

The patient was scheduled for a left orbitotomy with incisional biopsy that transformed into a complete surgical resection with margin based on the frozen section result. In addition, the left upper-lid biopsy was removed under general anesthesia 1 week later. Microscopic examination of the left orbital mass revealed a malignant spindle-cell tumor composed of pleomorphic and bizarre giant tumor cells embedded within an inflamed collagenous stroma with many reactive lymphoid aggregates. The tumor extended to the resection margin. Neoplastic cells were positive for CD34 and CD68, focally positive for S100, and negative for CD21, actin, desmin, STAT6, AE1/AE3, Melan A, SOX10, and GFAP. Ki-67 showed a nuclear labeling index of approximately 5%. Diagnosis was that of an undifferentiated pleomorphic sarcoma (UPS), likely postradiation (pT3NX). The left upper-lid biopsy demonstrated portions of a basal-cell carcinoma.

After his diagnosis of UPS, the patient underwent a positron emission tomography/computed tomography scan that showed no positron emission tomography evidence of nodal or osseous metastases. Two weeks later, the patient underwent right craniotomy with the transsylvian approach for resection of the right sphenoid wing and right cavernous sinus masses. The right sphenoid wing mass showed the presence of a meningioma with profound nuclear atypia typical of that described in radiation-induced meningiomas. It had a mitotic count of 3 per 10 high-power (×40 objective) fields. Atypical features included hypercellularity and prominent nucleoli. The lesion showed strong immunoreactivity for EMA and PR and had an elevated Ki-67 labeling index of 9.9%. The right cavernous sinus mass showed a spindle-cell neoplasm with variable cellularity and areas of compact (Antoni A) growth along with smaller areas of loose growth (Antoni B), and vague nuclear palisading (Verocay body formation). Mitotic figures were present but difficult to find. The tumor showed strong positivity for S100, SOX10, and p16INK4A. It was negative for CD34, STAT6, and epidermal growth factor receptor.

Fig. 1. **a** MRI of the orbit revealing a left orbital mass and an additional complex lobulated mass involving the right parasellar region, including the right sphenoid wing and right cavernous sinus (masses are indicated by blue arrows). **b** Resection specimen of the left orbital mass showing a malignant spindle cell tumor consisting of pleomorphic and bizarre giant cells embedded within an inflamed collagenous stroma with many reactive lymphoid aggregates. H&E. $\times 20$. **c** Higher magnification image of the pleomorphic

and bizarre cells. H&E. $\times 40$. **d** Resection specimen of the right sphenoid mass showing features of a meningioma (round uniform nuclei, lobulated architecture, meningothelial whorls and psammoma bodies) with profound nuclear atypia. H&E. $\times 20$. **e** Resection specimen of the right cavernous mass showing a spindle cell neoplasm with vague Verocay body formation. H&E. $\times 20$. **f** Left upper lid nodule is composed of a collection of basaloid cells with elongated hyperchromatic nuclei. H&E. $\times 20$.

At the patient's 4-month follow-up, he was doing well. He underwent radiotherapy for the intracranial tumors (schwannoma and radiation-induced meningioma), and is currently taking adjuvant pazopanib at 600 mg daily for the pleomorphic sarcoma of the left orbit. The tissue overlying the left eyelid basal-cell carcinoma has healed well and is without any residual abnormalities, why it is being closely followed. His vision has recovered, and currently, his visual acuity is 20/100 +1.

Discussion

Patients with hereditary retinoblastoma are at an increased risk for the development of secondary neoplasms. This is attributed to the presence of *RB1* germline mutations, treatment (radiotherapy), or a synergistic combination of these 2 factors [6]. Hereditary retinoblastoma

patients who undergo enucleation alone are at increased risk of developing a second malignancy when compared to the general population. Treatment with radiotherapy amplifies this risk, with individuals having a 51% risk for developing a secondary primary tumor 50 years after diagnosis and 13% risk for developing any soft-tissue sarcoma 50 years after radiotherapy. Increasing radiation dose and younger age at the time of radiotherapy increase a patient's risk of developing a secondary neoplasm. Patients who undergo radiotherapy during the first year of life are at increased risk for the development of a second neoplasm compared to patients who undergo radiotherapy after 1 year of age [7].

The occurrence of a secondary neoplasm in patients following treatment for retinoblastoma has been reviewed in several studies [8–11]. The most frequent second ma-

lignancies are leiomyosarcoma, osteosarcoma, and melanoma. UPS, schwannoma, and meningioma have been reported but are relatively rare in the setting of treated retinoblastoma [8–12]. A meta-analysis of 676 secondary tumors in patients with retinoblastoma demonstrated that the median age at diagnosis of all secondary tumors was 13.0 years (range, 0.3–60.4), 13.0 years for sarcoma, and 29.0 years for carcinoma [13].

UPS is a diagnosis that was introduced by consensus opinion in 2002 by the World Health Organization after it had been shown that many pleomorphic sarcomas (lesions previously diagnosed as malignant fibrous histiocytoma) could be meaningfully subclassified. UPS is a malignant tumor that is currently diagnosed by the lack of definable differentiation and is therefore a diagnosis of exclusion [14]. It has an incidence of 1–2 per 100,000 people and usually occurs as a deep-seated, painful lesion in the extremities and is rare in the orbit. The standard treatment for UPS is complete surgical resection with margins. UPS is considered aggressive and is characterized by rapid growth, local recurrence, and metastasis, most commonly to lung (90%) followed by bone (8%), and liver (1%). UPS associated with radiation has a worse overall survival and a higher rate of local recurrence than sporadic UPS [15].

UPS demonstrates considerable histological variation, and the diagnosis of UPS is based on the lack of differentiation by histology or by other ancillary studies, most commonly immunohistochemistry. As shown in this case, histological features of UPS include the presence of pleomorphic and bizarre tumor cells, often arranged in fascicles or embedded in a collagenous and inflamed stroma. Lack of differentiation separates UPS from other pleomorphic-appearing tumors, and important diagnoses to rule it out include pleomorphic variants of liposarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor, osteosarcoma, and other pleomorphic neoplasms. Histological features helpful in the exclusion of UPS include the presence of multivacuolated lipoblasts (pleomorphic liposarcoma), osteoid formation (pleomorphic extraskeletal osteosarcoma), blunt-ended nuclei focally arranged in fascicles (pleomorphic leiomyosarcoma), and large cells with abundant eosinophilic cytoplasm and cross striations (pleomorphic rhabdomyosarcoma). Pleomorphic malignant peripheral nerve sheath tumor usually requires observing the transformation of a benign nerve sheath tumor to its malignant component or tumor arising in a peripheral nerve in the setting of neurofibromatosis type 1.

Immunohistochemistry is particularly helpful in the diagnosis of UPS as immunoreactivity for smooth muscle markers (i.e., desmin, muscle-specific actin, and alpha smooth muscle actin) is usually typical of leiomyosarcoma, and positivity for skeletal muscle markers (desmin, MyoD1, and myogenin) is often characteristic of rhabdomyosarcoma. Immunohistochemistry can also be helpful in the exclusion of nonsarcomatous pleomorphic lesions such as melanoma (S100, Melan A, HMB45, and SOX10). It is important to correctly classify pleomorphic sarcomas, as studies have suggested myogenic differentiation may behave more aggressively and have shorter overall survival [16].

Subsequent craniotomy and resection discovered a radiation-induced meningioma (right sphenoid wing mass) and schwannoma (right cavernous sinus mass). Radiation-induced meningiomas are histologically characterized by profound nuclear atypia far exceeding that seen in usual meningiomas and arise after irradiation [17–19]. These tumors are not graded using current WHO criteria since features associated with benign behavior, such as the presence of positivity for progesterone receptor and low proliferation indices, do not correlate with benign behavior in patients with radiation-induced meningioma [20]. In addition, radiation-induced meningiomas have been found to have different molecular signatures from those occurring in meningiomas arising in the absence of radiation [21]. The age of presentation and the latency period for the development of a radiation-induced meningioma are dose related. Radiation-induced meningiomas have higher recurrence rates than their nonirradiated counterparts and often show multiplicity [18, 20].

The right cavernous sinus tumor showed the presence of a nerve sheath tumor with features of schwannoma. The tumor's low mitotic activity, strong retained immunopositivity for S100, SOX10, and p16INK4a, and the lack of epidermal growth factor receptor expression argue against malignant transformation. Histological features and the absence of STAT6 or CD34 positivity helped exclude solitary fibrous tumor/hemangiopericytoma. Current literature is limited as to the behavior of benign-appearing nerve sheath tumors in the setting of treated retinoblastoma. The left lid showed a basal-cell carcinoma; ionizing radiation is a known risk factor for the development of this neoplasm [22].

The occurrence of 4 different neoplasms within the irradiated field following radiation therapy for bilateral retinoblastoma is unique. Marees et al. [11] analyzed the long-term risk for the development of second malignan-

cies in retinoblastoma survivors and reported 4 patients (out of 668 total patients) who also developed a third malignancy. Diagnoses in these patients included soft-tissue sarcoma, skin melanoma, breast cancer, and lung cancer. In all of these patients, the third malignancy did not occur within the radiation field and differed from their second malignancy.

This case illustrates the importance of life-long surveillance for patients with hereditary retinoblastoma, particularly when treated with radiation. Currently, there is no established standard of care for long-term surveillance of irradiated retinoblastoma. Early detection allows a better chance for complete tumor resection with negative surgical margins, generally considered the most important prognostic factor related to increased survival for

UPS [7]. This is paramount since the leading cause of early related death in patients with hereditary retinoblastoma is due to a second malignancy.

Statement of Ethics

This case report meets the criteria set forth by the Office for the Protection of Research Subjects (OPRS) and Institutional Review Board (IRB) of the University of Southern California (USC).

Disclosure Statement

The authors of this article have no conflicts of interest to disclose.

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