Radiation-induced rhabdomyosarcoma of the brainstem in a patient with neurofibromatosis Type 2

Case report

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Neurofibromatosis Type 2 (NF2) is a rare, autosomal dominant disorder characterized by the development of benign tumors of the peripheral nervous system and the CNS, including schwannomas, meningiomas, and ependymomas. The gene responsible for the development of NF2 acts as a tumor suppressor gene. Stereotactic radiotherapy (SRT) or single-fraction stereotactic radiosurgery has been increasingly used in the past decades to treat benign tumors in patients with NF2. These radiotherapy methods are less invasive and can be potentially used to treat multiple tumors in a single session. The risk of inducing malignancy is unclear. Few reports exist of malignant peripheral nerve sheath tumors, meningiomas, or ependymomas occurring after SRT or stereotactic radiosurgery in patients with NF2. The authors present the first documented case of rhabdomyosarcoma following SRT for multiple NF2-associated schwannomas. Compared with patients with sporadic tumors, NF2 patients having a germline tumor suppressor gene defect may be more prone to secondary malignancies after treatment involving radiation therapy.

(DOI: 10.3171/2009.6.JNS09105)

Key Words • radiation-induced malignancy • stereotactic radiotherapy • neurofibromatosis Type 2 • rhabdomyosarcoma

Abbreviations used in this paper: ABI = auditory brainstem implant; NF2 = neurofibromatosis Type 2; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; VS = vestibular schwannoma.

See the corresponding erratum in this issue, p 209.
Case Report

History. In November 2006, a 25-year-old woman presented 13 years after an initial diagnosis of NF2. Her symptoms included rapidly progressive brainstem compression manifesting as 4-limb weakness, gait unsteadiness, right facial paralysis, breathing irregularities, dysarthria, and severe dysphagia. These necessitated both a tracheostomy and gastric tube placement.

In October 1993 at the age of 12 years, the patient was found to have bilateral VSs and underwent resection of the larger left lesion via a retrosigmoid approach. This initial surgery resulted in complete left-sided sensorineural hearing loss and total facial paralysis. In July 1995 at the age of 14 years, the patient underwent a right middle fossa decompression of the right internal auditory canal in an attempt to preserve hearing in her only functioning ear. One year later, the left VS was found to have recurred and there was symptomatic growth of the right VS; in June 1996, she underwent reoperation on the left side with a subtotal translabyrinthine resection of the tumor and placement of an ABI. Approximately 5 months later, she underwent SRT (total dose 5400 cGy in 27 fractions over 40 days) for treatment of the enlarging right VS. In June 1999, she also received SRT targeting the contralateral side (total dose 5040 cGy in 26 fractions over 40 days) for recurrent disease. The fields encompassed the greater part of the posterior fossa on the treated side and somewhat overlapped the brainstem. In 2002 when she was 20 years old, the patient underwent resection of the right VS due to continued tumor growth despite the SRT, and an ABI was placed.

Despite multiple operations and progressive disease, the patient exhibited a relative high functional status.

![Fig. 1. Axial Gd-enhanced T1-weighted MR images demonstrating a new homogeneously enhancing mass in the right cerebellomedullary fissure that was not present on earlier scans. The patient has numerous stable extraaxial schwannomas. Note the ABI lead (arrow) appears to be pushed off the brainstem by the tumor but continued to provide some auditory function, likely indicating that this is an intraaxial tumor.](image-url)
Nonetheless, at age 24 years (March 2006) and only 10 years after the first radiotherapy course targeting the right posterior fossa, she suffered precipitous neurological decline. Over the ensuing 5 months, she came to require complete support via a tracheostomy for nocturnal ventilation and gastric tube placement to preclude aspiration. An MR imaging study of the neural axis revealed a new, large tumor involving the inferior right medulla and cerebellomedullary cistern (Figs. 1 and 2). It was not entirely clear if it was intra- or extraaxial in origin. In addition, multiple schwannomas were unchanged from prior imaging 6 months earlier. These schwannomas involved the left jugular foramen, right oculomotor nerve, bilateral Meckel cave, right foramen rotundum, and multiple spinal nerve roots among others.

Examination and Operation. The patient returned to the Mayo Clinic Department of Neurosurgery in February 2007 and surgery was undertaken to establish the diagnosis of the new medullary region tumor and to decompress the brainstem. Exploration confirmed the presence of an intraaxial brainstem tumor. Given its extent and poorly defined margins, the tumor was only internally debulked. Examination of intraoperative frozen sections suggested a rhabdomyosarcoma. Examination of permanent sections confirmed the diagnosis of embryonal rhabdomyosarcoma (Fig. 3 left), with immunostains for desmin (DER11, 1/200 dilution; Dako) (Fig. 3 right) and myogenin (clone F5D, 1/500; Dako) being strongly positive. No nerve involvement or nerve sheath tumor precursor lesion was seen, with stains for S100 protein (polyclonal, 1/1600; Dako) and epithelial membrane antigen (E29, 1/50; Dako) being negative. Stains for the proliferation marker MIB-1 (MIB-1, 1/300; Dako) revealed a high labeling index. Ultrastructure analysis also confirmed the

![Image](image_url)
diagnosis, demonstrating large cells with numerous thick and thin parallel cytoplasmic filaments associated with Z-bands (Fig. 4). Postoperatively, the patient’s neurological condition remained unchanged.

Postoperative Course. Given the rarity of primary intracranial rhabdomyosarcoma and lack of a known association of this tumor with NF2, an extensive imaging evaluation was undertaken to seek a primary rhabdomyosarcoma elsewhere. Computerized tomography scanning of the chest, abdomen, and pelvis, as well as a ⁹⁹mTc–methylene diphosphonate whole-body scanning with SPECT, revealed no extracranial primary disease. Thus, the intracranial tumor appeared to be primary and to have developed in an irradiated field. Postoperative chemotherapy was considered, but, given the patient’s overall poor functional status, it was not pursued. Review of outside SRT records demonstrated significant overlap of radiation fields with the tumor bed from both her first and second course of SRT, and it was believed that additional radiation to her brainstem would lead to substantial further morbidity. In May 2007, 3 months after the diagnosis of rhabdomyosarcoma, the patient died. Genetic analysis of the rhabdomyosarcoma tumor demonstrated a normal karyotype. No NF1 mutation was found in the lymphocytes. Comprehensive cytogenetic analysis at 550-band resolution demonstrated a normal karyotype. The NF2 mutation analysis of lymphocytes showed a constitutive deletion involving the NF2 promoter region and exon 1, (c.-431?_c.46+?del). No “second-hit” NF2 mutation was found by analysis of the DNA extracted from the rhabdomyosarcoma, further suggesting that the malignancy did not arise from a preexisting VS.

Discussion

Primary Versus Radiation-Induced Carcinogenesis

An inherent challenge in cases such as ours is determining the frequency of radiation-induced malignancies, particularly establishing whether the tumor developed as a result of ionizing radiation or simply as an independent primary lesion. In an attempt to lend clarity, Cahan et al.7 established criteria by which sarcomas could be reasonably considered radiation induced. Since that time, criteria have been further modified to accommodate a broader range of tumor types.1 To be deemed radiation induced by the modified Cahan scheme, the following criteria must be met: 1) the new tumor must arise within the previous field of radiation; 2) there must be histological and imaging evidence of the preexisting condition in addition to microscopic proof of a tumor; 3) the second tumor must be of a different histological type from the first lesion to exclude the possibility of a simple recurrence; and 4) a sufficient latency period (> 5 years) must have passed between the time of radiation and the development of the second tumor. The present case of brainstem rhabdomyosarcoma fulfills all the required criteria.15 Isodose curve analysis for both courses of radiation overlapped with the location of the rhabdomyosarcoma. Serial MR imaging showed the original and postirradiation lesions to reside at somewhat different locations. In addition, histological and genetic analyses confirmed the very different natures of the tumors (VS and intraparenchymal rhabdomyosarcoma). The latency periods (10 and 8.5 years, respectively) from the first and second courses of SRT were appropriate in length. Sporadic intracranial rhabdomyosarcoma is very uncommon. Fewer than 40 cases have been described in the literature.13 Postirradiation rhabdomyosarcoma is
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even less common.34 Lastly, an extracranial source of the rhabdomyosarcoma is highly improbable given the negative chest, abdominal, and pelvis CT scans and the negative whole-body nuclear medicine study.

Neurofibromatosis Type 2 Tumorigenesis and Effects of Radiation

In a review of the literature, we identified only 13 cases of histologically verified intracranial malignancies occurring in stereotactic radiation fields.4,5,10,21,29,40–43,48,52 The authors of a recent letter discussed 5 additional patients with NF2 who, after SRT, developed malignant tumors in high-dose areas.6 Because this report does not discuss radiation dosing, timing of malignancy after radiation, and histological authentication, we have chosen to exclude these patients from our analysis. While only a small fraction of patients with VS undergoing radiation have NF2, 3 of these 13 published cases involved such patients.5,10,48 Within this NF2 subset, all 3 patients had primary malignant degeneration of a VS following radiotherapy whereas none involved secondary malignancy (Table 1).

As experience with radiotherapy in the management of NF2-associated lesions increases, evidence is emerging that a significantly higher incidence of benign and malignant tumors follows upon treatment. In non-NF2 patients, an 18.8-fold increased relative risk of schwannoma induction follows radiation doses of as little as 2.5 Gy.39 Particularly relevant to our case is the > 10-fold increased risk of developing a malignant tumor in irradiated as opposed to nonirradiated NF2 cases.6 Although ~4% of all VSs occur in patients with NF2, ~50% of all examples of postirradiation malignant transformations of schwannomas occur in this population.4 One possible explanation for the disproportionate increase in the frequency of malignant transformation of schwannomas in NF2 tumors may simply be that patients with NF2 can develop many more schwannomas. The radiation dose to a schwannoma, which is often unsuccessful in complete tumor destruction, and the falloff close to surrounding tissue in which additional tumor(s) may reside may also contribute to malignant transformation.12,36,48 Radiation-induced mutations, such as of TP53, are well known to produce malignant tumors, a process incorrectly termed “malignant degeneration.” With respect to schwannomas, their occurrence is supported by the observation that SRT-treated tumors removed from radiotherapy-treated patients with NF2 have more chromosomal anomalies than those not similarly treated.50

Strictly defined by modified Cahan criteria,1,7 our patient had developed a postirradiation intracranial embryonal rhabdomyosarcoma. Rhabdomyosarcomas are the most common soft-tissue sarcomas of childhood and adolescence. They appear to arise from pluripotent mesenchymal cells, often at sites that do not contain skeletal muscle; most affect the extracranial head and neck region and genitourinary tract. Their intracranial development is exceedingly rare;8,15,25,33,47,53 such tumors carry a grave prognosis, with survival rarely exceeding 2 years.8 The molecular pathogenesis of embryonal rhabdomyosarcoma is well studied. Most studies have focused on the role of loss or rearrangement of chromosomes 11 and 15.38 Yet other studies have shown possible alterations in several important cell-signaling pathways, including Ras-activating mutations, p53 pathway alterations, retinoblastoma protein cell cycle deregulation, and MYCN amplification.24,51

The underlying molecular cause of the radiation-induced rhabdomyosarcoma in our patient is unknown and could possibly be similar to radiation-induced abnormalities in other tumor systems such as postirradiation gliomas,46,49 meningiomas,16,26 and malignant peripheral nerve sheath tumors.30 In our patient, the underlying germline NF2 mutation may also predispose to the development of postirradiation neoplasia, perhaps due to Ras or AKT pathway abnormalities, which have been implicated in the tumorigenesis of both benign NF2-associated schwannomas and rhabdomyosarcomas.9,20,24 Further study is needed to validate these hypotheses.

Conclusions

In summary, SRT and SRS remain attractive therapeutic options for patients with both sporadic and syndromic VSS. Over the last decade evidence has emerged

TABLE 1:  Histologically verified reports of postirradiation malignancies in patients with NF2*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Radiation Modality</th>
<th>Original Pathological Type</th>
<th>Yrs to Malignancy</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noren, 1998</td>
<td>18, F</td>
<td>GKS</td>
<td>acoustic neuroma</td>
<td>6</td>
<td>MNST</td>
</tr>
<tr>
<td>Thomsen et al., 2000</td>
<td>19, F</td>
<td>GKS</td>
<td>acoustic neuroma</td>
<td>6</td>
<td>anaplastic meningioma (meningiosarcoma)</td>
</tr>
<tr>
<td>Bari et al., 2002</td>
<td>28, F</td>
<td>GKS</td>
<td>acoustic neuroma</td>
<td>4</td>
<td>MNST</td>
</tr>
<tr>
<td>present case</td>
<td>25, F</td>
<td>FSRT</td>
<td>acoustic neuroma</td>
<td>10</td>
<td>rhabdomyosarcoma</td>
</tr>
</tbody>
</table>

* FSRT = fractionated SRT; GKS = Gamma Knife surgery; MNST = malignant nerve sheath tumor.
indicating an increased risk of malignancy following radiotherapy, particularly in the population of patients with NF2. During pretreatment consultation, patients should be counseled regarding the risk, albeit small, of developing a radiation-induced cancer. While our findings do not argue against the use of SRT, they should heighten the awareness of postirradiation neoplasia and the need for individualized treatment.

**Disclaimer**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**References**


M. L. Carlson et al.
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Manuscript submitted January 23, 2009. Accepted June 2, 2009. Please include this information when citing this paper: published online July 3, 2009; DOI: 10.3171/2009.6.JNS09105.

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