Late malignant transformation of vestibular schwannoma in the absence of irradiation: case report

Asma Bashir, MD, Lars Poulsgaard, MD, Helle Broholm, MD, PhD, FRCS, and Kåre Fugleholm, MD, PhD

Departments of Neurosurgery and Pathology, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Late malignant transformation of vestibular schwannoma (VS) following irradiation has previously been reported 29 times in the literature. Here, the authors report the first late malignant transformation of VS unrelated to neurofibromatosis or radiation exposure. After undergoing a near-total excision of a histologically benign VS, the patient developed malignant regrowth of the tumor remnant 42 months after the primary excision. This case challenges the dogmatic belief of absolute causality between radiation exposure and late malignant transformation of VS, and has important implications regarding future counseling and consent for the treatment of patients with VS.

http://thejns.org/doi/abs/10.3171/2015.6.JNS1544

KEY WORDS vestibular schwannoma; tumor recurrence; MIB-1 index; malignant transformation; malignant peripheral nerve sheath tumor; oncology

Malignant transformation of vestibular schwannoma (VS) following irradiation has previously been reported 29 times in the literature with a mean delay of 85 months after the treatment. Here, we present the first case of late malignant transformation of benign VS in a patient with no history of neurofibromatosis Type 2 (NF2) or previous radiation exposure, and in a window of time comparable with that observed for malignant transformation after irradiation.

Case Report
History and Examination
In August 2010, a 47-year-old female patient presented with a 6-month history of right-sided gradual hearing loss, tinnitus, and balance disturbance, and a 10-month history of right facial numbness. The patient had neither a family history nor features of NF2, or any history of radiation exposure. Neurological examination revealed decreased sensation on the right side of her face involving the first and second branches of the trigeminal nerve, sensorineural hearing loss, and a positive Romberg’s test. Caloric testing showed abolished vestibular function on the right side. MRI of the brain demonstrated a contrast-enhancing mass, with a size of 31 mm in the largest extrameatal diameter, in the right cerebellopontine angle, and a slightly enlarged meatus (Fig. 1A).

Operation and Histological Examination
The patient underwent a near-total tumor excision via a translabyrinthine approach. The tumor tissue was adherent...
Malignant transformation of vestibular schwannoma
to the facial nerve, and a small remnant of the tumor was left behind on the nerve. After surgery, the patient exhibited a right-sided facial nerve palsy (House-Brackmann Grade IV) and was discharged home 5 days later. Histo-

logically, the tumor tissue was typically biphasic and was composed of glial fibrillary cells. These were arranged in interlacing fascicles, sometimes with nuclei aligned in a palisading pattern (but with no characteristic Verocay bodies), and intermingled with a more cystic glial tissue. Positive immunoreactivity for S100 protein was present universally, and MIB-1 labeling index was less than 2% (Fig. 2A–E). The histological diagnosis was a typical benign VS, WHO Grade I.

Postoperative Radiological Surveillance
Six months later, MRI showed a small residual tumor on the brainstem near the cerebellar peduncle (Fig. 1B). At this stage, the patient had regained facial nerve function (House-Brackmann Grade II). We decided to monitor the patient with serial MR images, which showed no change in the residual tumor size the following 24 months (Fig. 1C). The patient did not receive radiation treatment.

Tumor Recurrence and Second Operation
In February 2014, 42 months after the primary excision, the patient developed a right-sided facial paralysis (House-Brackmann Grade VI) over a period of 2 months. Now, MRI revealed progression in size of the residual tumor, measuring 10 × 10 mm and deeply embedded in the cerebellar peduncle (Fig. 1D). A second translabyrinthine tumor excision was performed. As the facial nerve was infiltrated by tumor tissue and the frozen section analysis suggested malignancy, the tumor was completely excised including a section of the facial nerve. Postoperatively, the patient recovered quickly and was discharged from the hospital 3 days later with facial nerve paralysis. Histological examination now demonstrated a tumor tissue of an infiltrative nature with hypercellularity and focally pleomorphic cells in a fascicular arrangement. There were 15–20 mitoses per 10 hpf, with the MIB-1 labeling index of up to 50% in some areas. The immunoreactivity for S100 protein was only positive focally (Fig. 3A–F). Furthermore, immunohistochemistry for p53 showed strong diffuse staining in the tumor tissue, indicating enhanced expression of mutant p53 protein (Fig. 3G and H), but not in the tumor obtained at first resection (Fig. 2F). The features resembled a sarcomatous change, and the final histological diagnosis was a malignant peripheral nerve sheath tumor (MPNST).

Stereotactic Radiotherapy and Outcome
A month after the second excision, the patient underwent a hypoglossal-facial nerve anastomosis to reanimate her face. The patient was then referred to another center for adjuvant stereotactic radiotherapy (SRT) to the tumor bed (1.8 Gy per fraction, 30 fractions total). At the time of irradiation, no visible tumor mass was seen on MRI (Fig. 1E). The patient tolerated the treatment well and completed it by the end of June 2014. Since then, the patient has been followed in the outpatient clinic with clinical evaluations and MRI scans every 3 months. The patient has been clinically stable as of this writing, apart from complaints of occasional dizziness, and without any signs of tumor recurrence 9 months after irradiation as assessed by serial MRI (Fig. 1F–H).

Discussion
Malignant transformation of a histologically benign VS is extremely rare. To our knowledge, the present case is
The first histologically confirmed report of late malignant transformation of a previously benign VS with no predisposing factors such as NF2 or previous irradiation. In the published literature, a total of 20 cases of malignant VS in the absence of aforementioned risk factors have been reported (Table 1). Of these, only 4 cases have been reported with a benign histology of VS before undergoing malignant transformation. Two of these cases deserve special attention. Son et al. described histological features consistent with early malignant progression from a benign VS. They confirmed the benign nature of VS histologically before it transformed into a malignant schwannoma after only 2 months in contrast to the latency of 42 months in our case. One might suggest that the primary tumor in the case of Son et al. had both malignant and benign components. However, due to a possible sampling error of the first tumor specimen, the malignant component was not discovered histologically, and therefore, a rapid recurrence was observed 2 months later. Postoperative scanning consisted of CT scanning only, and not MRI. This might explain the recurrence, and thus enlargement of a possible residual tumor, as CT scanning is insufficient to verify gross tumor excision. McLean et al. were the first to report malignant transformation of VS after initial surgery. However, small areas of malignant characteristics including increased cellular density and mitotic figures were already present in the histological examination of the primary VS. Hence, this schwannoma might have been malignant from the outset.

It has previously been suggested that an elevated MIB-1 labeling index (normal range < 2%) might reflect a predisposition for malignant transformation and might correlate with a high risk of regrowth of tumor after partial or near-total resection. Neither of the above-reported studies and cases reported by Scheithauer et al. mentioned the MIB-1 index of the primary tumor. Son et al. reported scattered MIB-1–positive cells with an index of the first and second recurrent tumor constituting 3% and 2%, respectively. This is remarkable because of the rapid tumor growth within a very short time frame, similar to the behavior of a “biologically aggressive” schwannoma.
In our case study, the MIB-1 labeling index was less than 2%, confirming the benign nature of the primary tumor, thus indicating a favorable prognosis.

In recent years, the use of stereotactic radiosurgery (SRS) or SRT has been shown to be an effective alternative to microsurgical removal of most small- to medium-sized VSs with tumor control rates as high as 97%, with preservation of nerve function and minimum risk of damage to surrounding neuronal structures. However, there is a concern that irradiation itself might play a causative role in secondary malignancy, which is a rare but a serious complication after radiation treatment, as reported in several case reports. In a large study of 440 patients treated with Gamma Knife surgery for VS and with a median follow-up period of 12.5 years, the authors reported only one case of developing malignant change. The overall malignant transformation rate was calculated to 0.3%, with an annual incidence of 0.02%. However, there was no histological confirmation of the tumor type before irradiation. Patel and Chiang reviewed 36 cases of SRS-induced neoplasms, half of them having initial diagnosis of VS (n = 22). Thirteen of these VSs transformed into MPNST, 5 developed glioblastoma, and the remaining were sarcomas. The authors estimated the risk of developing a malignancy after SRS for any benign lesion to be 0.04% at 15 years postirradiation. Until recently, there has been no accurate quantification of the risk of malignant transformation of irradiated versus nonirradiated VSs. In a recent review by Seferis et al., the authors estimated that the overall risk of malignancy over 20 years in cases in which radiation treatment has occurred was 15.6 per 100,000 (0.016%), while this risk decreased to 1.09–1.74 per 100,000 (0.001%–0.002%) in cases of no radiation exposure. However, the true incidence of radiation-induced neoplasms is rather difficult to estimate, given the individual case reports with different sources of radiation, total radiation dose, and number of treatments, lack of histopathology of the primary tumor, and a postradiation follow-up period of less than 15 years.

Traditionally, to be considered a radiation-induced malignancy, the tumor must fulfill Cahan’s criteria, which included: 1) the new tumor must occur within the previously irradiated field, and should not be present at the time of irradiation; 2) a sufficient latency period is required between the time of irradiation and development of the new tumor; 3) the new tumor is Malignant transformation of vestibular schwannoma

### TABLE 1. Published papers on malignant VS in the absence of NF2 and radiation exposure

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Location</th>
<th>Primary Pathology</th>
<th>Secondary Pathology</th>
<th>Latency</th>
<th>Management</th>
<th>Outcome (survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kudo et al., 1983</td>
<td>54, M</td>
<td>Rt CN VIII</td>
<td>MPNST</td>
<td>Surgery</td>
<td>1 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernanz-Schulman et al., 1986</td>
<td>2, F</td>
<td>NA CN VIII</td>
<td>MPNST</td>
<td>Surgery</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best, 1987</td>
<td>24, F</td>
<td>Rt CN VIII</td>
<td>Triton</td>
<td>Surgery</td>
<td>4 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLean et al., 1990</td>
<td>75, M</td>
<td>Rt CN VIII</td>
<td>Acoustic neurilemoma w/ malignant features, MIB-1 NA</td>
<td>MPNST</td>
<td>11 mos</td>
<td>Surgery</td>
<td>2 mos</td>
</tr>
<tr>
<td>Matsumoto et al., 1990</td>
<td>59, M</td>
<td>Rt CN VIII</td>
<td>MPNST</td>
<td>Surgery</td>
<td>5 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han et al., 1992</td>
<td>47, F</td>
<td>Rt CN VIII</td>
<td>Triton</td>
<td>Surgery</td>
<td>11 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maeda et al., 1993</td>
<td>38, M</td>
<td>Rt CN VIII</td>
<td>Triton</td>
<td>Surgery</td>
<td>3 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mrak et al., 1994</td>
<td>40, M</td>
<td>Lt CN VIII</td>
<td>Malignant VS</td>
<td>Surgery + irradiation</td>
<td>36 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earls et al., 1994</td>
<td>77, M</td>
<td>Lt CN VIII</td>
<td>Malignant melanotic schwannoma</td>
<td>Surgery</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gruber et al., 1994</td>
<td>61, F</td>
<td>Rt CN VIII</td>
<td>Malignant VS</td>
<td>Surgery</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saito et al., 2000</td>
<td>69, M</td>
<td>Lt CN VIII</td>
<td>MPNST</td>
<td>Surgery</td>
<td>Stable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harada et al., 2000</td>
<td>7, M</td>
<td>Rt CN VIII</td>
<td>Acoustic schwannoma w/ few mitotic figures, MIB-1 2.3%</td>
<td>NA*</td>
<td>9 mos</td>
<td>Surgery + irradiation</td>
<td>NA</td>
</tr>
<tr>
<td>Son et al., 2001</td>
<td>33, F</td>
<td>Lt CN VIII</td>
<td>VS, MIB-1 NA</td>
<td>Malignant schwannoma</td>
<td>2 mos</td>
<td>Surgery + irradiation</td>
<td>Stable</td>
</tr>
<tr>
<td>Gonzalez et al., 2007</td>
<td>43, F</td>
<td>Lt CN VIII</td>
<td>Malignant VS</td>
<td>Surgery + irradiation</td>
<td>8 mos</td>
<td></td>
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<tr>
<td>Chen et al., 2008</td>
<td>62, F</td>
<td>Lt CN VIII/M/VIII</td>
<td>MPNST</td>
<td>Surgery</td>
<td>4 mos</td>
<td></td>
<td></td>
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<tr>
<td>Scheithauer et al., 2009</td>
<td>56, M</td>
<td>Rt CN VIII</td>
<td>VS w/ degenerative changes, MIB-1 NA</td>
<td>MPNST</td>
<td>7 mos</td>
<td>Surgery</td>
<td>2 mos</td>
</tr>
<tr>
<td>67, M</td>
<td>Rt CN VIII</td>
<td>VS, MIB-1 NA</td>
<td>MPNST</td>
<td>9 mos</td>
<td>Surgery</td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td>5, M</td>
<td>Lt CN VIII</td>
<td>MPNST</td>
<td>Surgery</td>
<td>Stable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karami et al., 2011</td>
<td>23, F</td>
<td>Lt CN VIII</td>
<td>MPNST</td>
<td>Surgery + irradiation</td>
<td>27 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wei et al., 2012</td>
<td>41, F</td>
<td>Rt CN VIII</td>
<td>MPNST</td>
<td>Surgery</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present case</td>
<td>47, F</td>
<td>Rt CN VIII</td>
<td>VS, MIB-1 &lt;2%</td>
<td>MPNST</td>
<td>42 mos</td>
<td>Surgery + irradiation</td>
<td>Stable</td>
</tr>
</tbody>
</table>

CN = cranial nerve; NA = not available. * MIB-1 before and after irradiation constituting 4.6% and 14.7%, respectively.
histologically distinct from the primary tumor; and 4) the patient should not have a genetic predisposition for cancer development. Several case reports lack a histological diagnosis of the primary tumor prior to irradiation.\textsuperscript{1,7, 22, 30} It might be due to the fact that the primary diagnosis is often presumptive, based on the imaging characteristics of the tumor only, and SRS or SRT is performed as a primary treatment without any histological investigation. This can increase the risk of an erroneous diagnosis of the irradiation-induced malignant transformation of the tumor. In 2 case reports, malignant transformation occurred only 6 months after SRS.\textsuperscript{13, 28} The short latency period in these cases could indicate that a malignant component already existed prior to irradiation, and might be aggravated by it, as radiation-induced malignancy usually develops over a longer period of time.\textsuperscript{1,7, 22, 30} However, there is no consensus on the minimum latency period between radiation exposure and tumor development, and further work is necessary to establish a reference latency interval for radiation-induced tumors. Finally, in some case reports, patients with malignant VS have underlying NF2, a genetic condition known to be associated with a higher risk of malignant tumors, especially after radiation treatment,\textsuperscript{2, 3, 22} and which contests Cahán’s Criterion.\textsuperscript{4} Baser et al.\textsuperscript{2} surveyed 1348 patients with NF2 and reported that patients with NF2 had a 14-fold increased risk of developing malignant brain tumors after irradiation compared with patients without NF2. Tanbouzi Hussein et al.\textsuperscript{3, 22} suggested that irradiation could serve as a final genetic hit that might induce a second tumor or malignant transformation in already mutated cells.

The causal association between irradiation and secondary transformation of VS has not clearly been demonstrated. The malignant transformation in the absence of irradiation in our case raises the question of whether the rare malignant transformation seen after radiation exposure represents a natural course of the disease rather than an effect of radiation exposure.

Conclusions

The present report is the first histologically confirmed case of late malignant transformation of VS in the absence of NF2 and previous irradiation, where a benign VS spontaneously became malignant with a latency period similar to that observed for malignant transformation after irradiation. Our case challenges the dogmatic belief of absolute causality between irradiation and late malignant transformation of VS and has important implications for future counseling and consent for treatment of patients with VS. We believe that rare case reports of secondary malignancy following irradiation should not deter physicians from its use, but caution is required when counseling patients, particularly young patients, with a genetic predisposition to cancers.

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

Author Contributions
Conception and design: Fugleholm, Bashir, Poulsgaard. Acquisi tion of data: Bashir. Analysis and interpretation of data: Bashir, Broholm. Drafting the article: Bashir. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fugleholm.

Correspondence
Kåre Fugleholm, Department of Neurosurgery, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 9, Copenhagen 2100, Denmark. email: kaare.fugleholm.buch@regionh.dk.