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

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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.

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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.²⁸ 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

ABBREVIATIONS MPNST = malignant peripheral nerve sheath tumor; NF2 = neurofibromatosis Type 2; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; VS = vestibular schwannoma.

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FIG. 1. Axial T1-weighted MR images showing a contrast-enhancing VS in the right cerebellopontine angle at the time of diagnosis (**A**), the residual tumor 6 months after the first operation (arrow, **B**), the residual tumor 24 months later (arrow, **C**), and tumor enlargement 42 months later (arrow, **D**); and absence of tumor after the second operation (**E**), 3 months after irradiation (**F**), 6 months after irradiation (**G**), and 9 months after irradiation (**H**).

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. Histologically, 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

FIG. 2. Histological examination of primary tumor resection showing an ordinary VS with long glial cells, fascicular orientated with numerous intermingled macrophages (A, H & E), universal positivity for S100 protein (B) with both Antoni A and Antoni B areas and characteristic hyalinized vessels (C, H & E); a higher magnification of the tumor from a more compact area (Antoni A pattern), with characteristic long Schwann cells with normochromatic nuclei, and an eosinophilic cytoplasm with indistinct borders (D, H & E); an MIB-1 labeling index less than 2% (E, Ki 67); and negative immunostaining for p53 (F). Original magnification $\times 50$ (A, B, and E); $\times 200$ (C, D, and F). Figure is available in color online only.

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).^{3,5,8,10–12,14,16,17,19,21,23–25,27,29,31,33} Of these, only 4 cases have been reported with a benign histology of VS before undergoing malignant transformation.^{24,29,31} Two of these cases deserve special attention.^{24,31} Son et al.³¹ 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.³¹ 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.²⁴ were the first to report malignant

FIG. 3. Histological examination of recurrent tumor, a highly cellular pleomorphic tumor (A, H & E) with many mitoses (B, H & E) and clear invasion in the surrounding parenchyma (C, H & E) and only sparse positivity for S100 protein in the tumor tissue (D, S100). The same area showing the brain parenchyma like islands surrounded by tumor tissue (E, GFAP); MIB-1 index constituting up to 50% (F, Ki 67); and diffuse positive immunostaining for p53, suggesting expression of mutant p53 (G and H). Original magnification $\times 50$ (A); $\times 200$ (B, C, and G); $\times 100$ (D–F); $\times 400$ (H). Figure is available in color online only.

transformation of VS after initial surgery. However, small areas of malignant characteristics including increased cellularity 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.^{9,34} Neither of the above-reported studies^{24,31} and cases reported by Scheithauer et al.²⁹ mentioned the MIB-1 index of the primary tumor. Son et al.³¹ 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.¹⁸

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

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

CN = cranial nerve; NA = not available.

* MIB-1 before and after irradiation constituting 4.6% and 14.7%, respectively.

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.^{6,15,20} 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.^{1,7,20,30,34} 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.¹⁵ Patel and Chiang²⁶ 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.,²⁸ 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,⁴ established in 1948, 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

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.^{15,30} 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.^{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.^{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,^{2,32} and which contests Cahan's Criterion 4.⁴ Baser et al.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 Husseini et al.³² 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, Poulsen. Acquisition 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.

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