CASE REPORT

Malignant Transformation of Acoustic Neuroma/Vestibular Schwannoma 10 Years after Gamma Knife Stereotactic Radiosurgery

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ABSTRACT

Only a handful of cases of de-novo malignancies of the vestibulocochlear nerve have been reported. Even rarer is the malignant transformation of a previously histologically diagnosed benign vestibular schwannoma. We present the case of a young adult who had combined operative/Gamma knife treatment for a benign vestibular schwannoma, followed by further surgery 2 years later. He represented 10 years after original diagnosis with facial numbness and ataxia, MRI showing gross tumor recurrence. After radical resection, histology showed malignant transformation to a malignant peripheral nerve sheath tumor. Within 3 months there was rapid, aggressive recurrence with brainstem compression, requiring further surgery for brainstem decompression. Histology confirmed further de-differentiation to an anaplastic sarcoma. While awaiting radiotherapy the tumor recurred again, the patient succumbing. The patient had no features of neurofibromatosis type 2. In the literature there are 13 other cases of malignant vestibular schwannomata. Only six had radiotherapy and of these only two had histological confirmation of a benign lesion preradiotherapy. Neither of these had neurofibromatosis. Three other cases had histological proof of malignancy postradiosurgery, but with no preradiotherapy histology; of these, two were positive for neurofibromatosis. The tumor biology of vestibular schwannomata as well as the radiobiology in the context of malignant transformation is discussed.

KEYWORDS: Vestibular schwannoma, acoustic neuroma, malignant transformation, malignant peripheral nerve sheath tumor (MPNST), anaplastic sarcoma, Gamma knife radiosurgery, radiotherapy

A malignant tumor of the vestibulocochlear nerve is extremely rare. Only a handful of cases of de novo malignancies exist in the literature. Even rarer is the malignant transformation of a previously diagnosed benign vestibular schwannoma. It has been previously postulated that the presence of neurofibromatosis type 2 (NF2) is a risk factor, but a recent series of Gamma Knife Surgery (GKS) in patients with vestibular schwannomas and NF2 from Pittsburgh showed no radiosurgery-associated secondary or malignant

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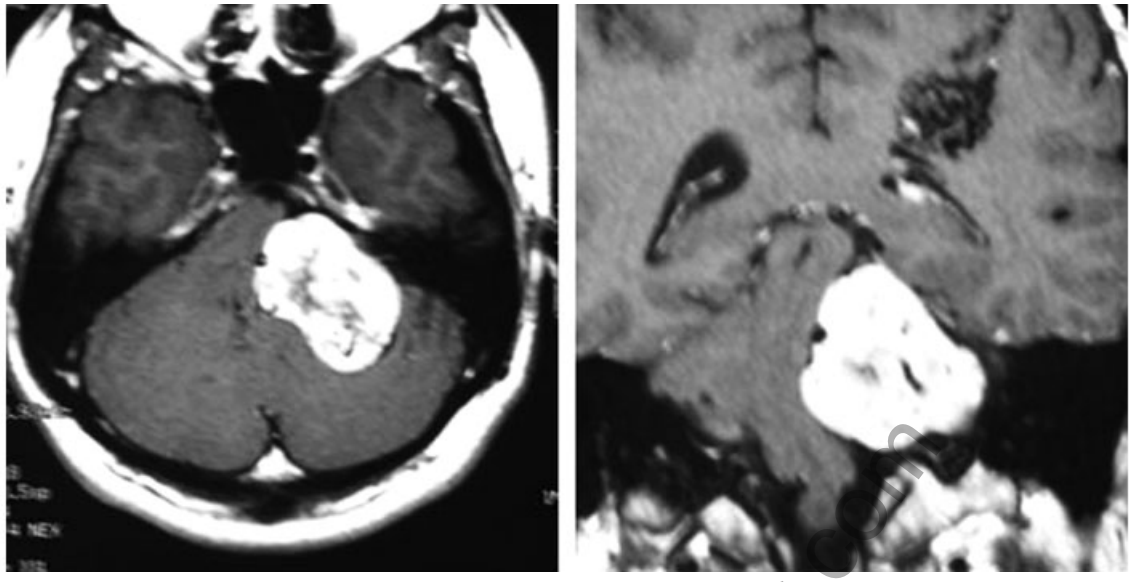

Figure 1 Axial CT (A) and Coronal T1W MRI (B) with contrast showing a left-sided cerebellopontine angle causing brainstem compression, at the time of initial presentation (1997).

tumors.[1] The experience from the National Centre for Stereotactic Radiosurgery in Sheffield shows no increased risk of malignancy after GKS; only one astrocytoma was detected after GKS for a cavernoma in a series of 4877 patients, which included 856 cases of vestibular schwannomas.[2] However, there are case reports of postradiation malignancy both at the site of radiation[3] and elsewhere in the brain,[4] with or without NF2. Although the use of GKS for vestibular schwannomas is becoming widespread, the presence of such cases, both at 6 years after GKS, questions the reassurance the above studies from Pittsburgh and Sheffield confer, where the follow-up was of a median of 53 months[1] and of a mean of 3.8 ± 3.0 years.[2] We present a case of malignant transformation of a vestibular schwannoma to a malignant peripheral nerve sheath tumor (MPNST) 10 years after the original diagnosis and GKS.

CASE REPORT

A 27-year-old male patient of Asian origin presented in 1997 with left-sided facial numbness and balance disturbance. Imaging showed a 4.5-cm left-sided cerebellopontine angle tumor suggestive of an acoustic neuroma (Fig. 1A, B). There was also a deep-seated left parietal arteriovenous malformation (AVM) (Fig. 2). He was treated surgically with partial resection of the acoustic neuroma, this being complicated by excessive bleeding associated with raised venous pressure due to the AVM. Gamma knife treatment was delivered to the residuum of the acoustic neuroma (15 Gy to 50% isocontour and 9 Gy to brainstem) and 6 months later to the AVM. Symptoms recurred in 1999 coupled to a radiological increase in tumor size (Fig. 3A), and a second resection was undertaken. Histology on both occasions confirmed a vestibular schwannoma (Grade I) with no features of atypia (Fig. 5A) and the universal presence of S100 protein. The AVM was further treated with interventional procedures and was eventually ablated.

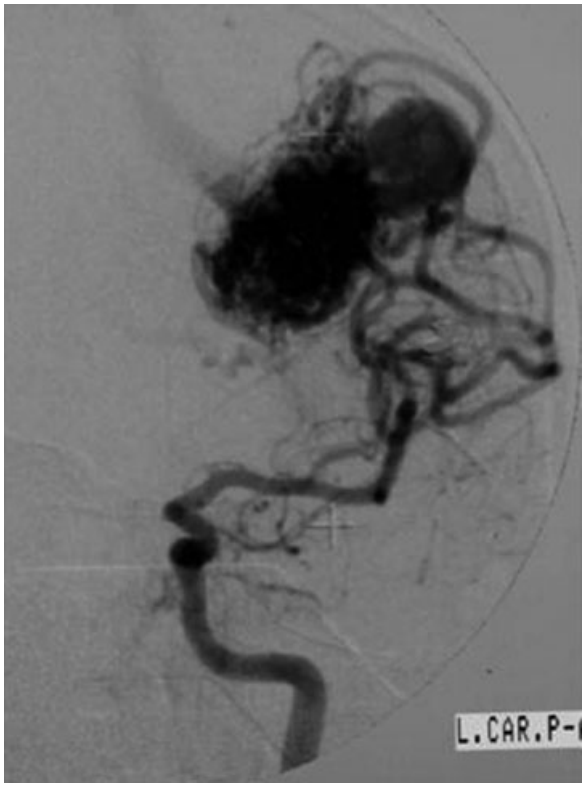

Figure 2 Digital subtraction angiography, left carotid injection, showing a deep-seated left parietal arteriovenous malformation (AVM) (1997).

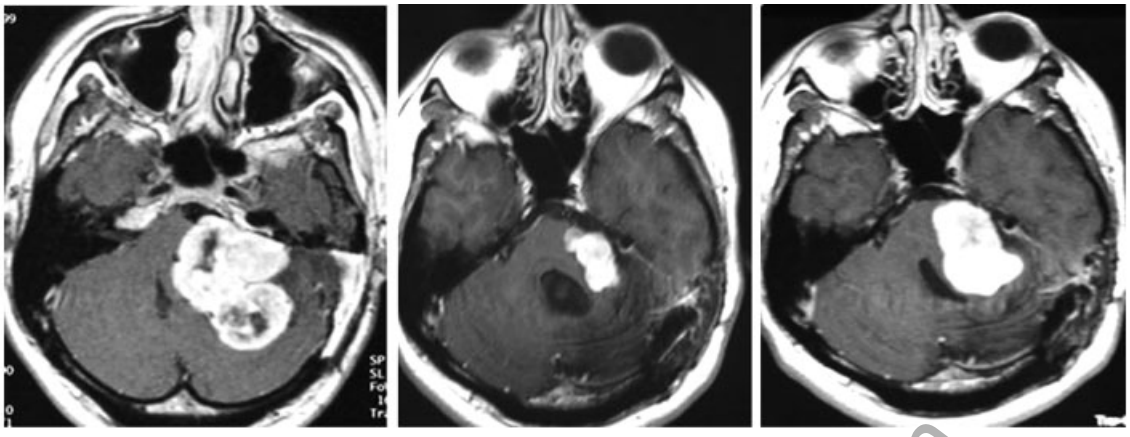

Figure 3 (A) Axial T1W MRI with contrast showing radiological recurrence consistent with symptomatic recurrence 2 years after original treatment (1999). At this time revision surgery was undertaken. (B) Stable radiological appearances in 2006. (C) In May 2007, when the patient re-presented with facial numbness and ataxia, MRI showed significance recurrence.

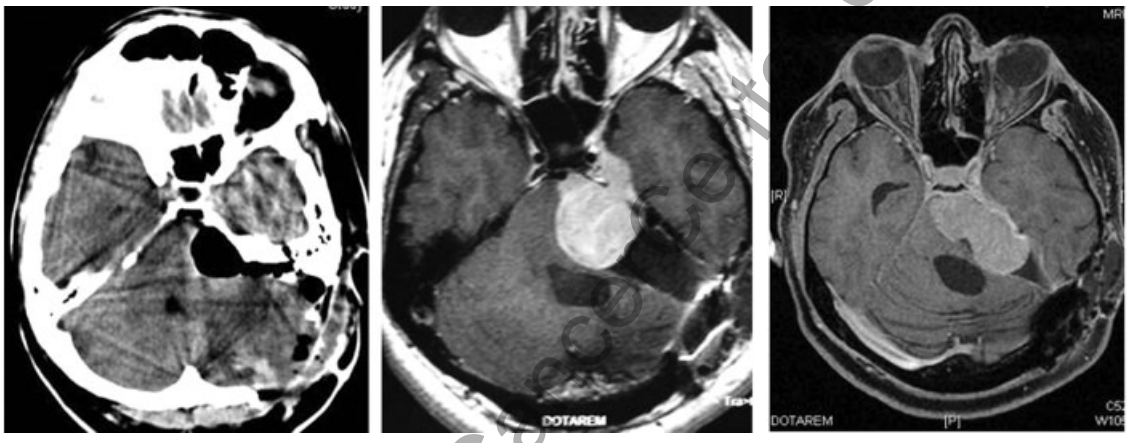

Figure 4 (A) Axial CT after radical re-resection was undertaken in May 2007. (B) Rapid and aggressive recurrence within 3 months of surgery, leading to another operative resection against symptomatic brainstem compression. (C) Yet again aggressive regrowth of the residual tumor within a month of the last operation with significant brainstem compression that proved to be fatal.

Annual radiological surveillance showed no change in residual tumor size. In October 2006, the patient developed a progressive left facial palsy after facial herpes. MRI showed a stable tumor (Fig. 3B) and the diagnosis of Ramsay Hunt syndrome was considered. In May 2007, he presented again with facial numbness and ataxia and MRI showed a gross tumor enlargement (Fig. 3C). Radical resection was

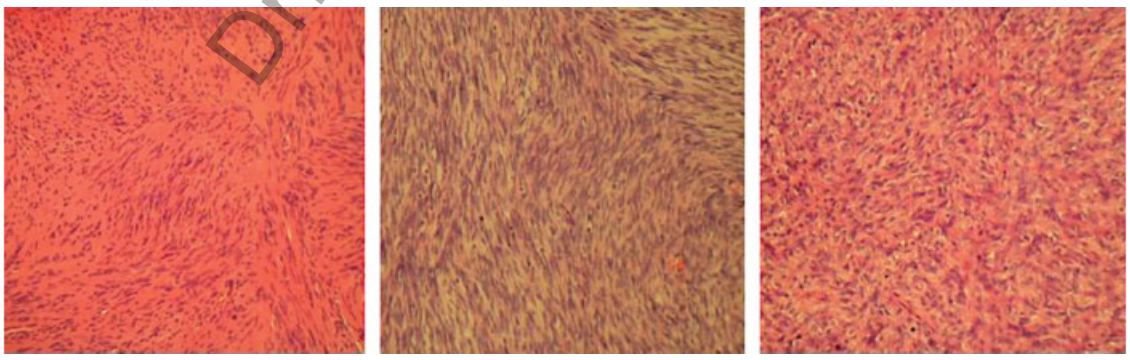

Figure 5 (A) Initial biopsy demonstrating sheets of streaming small fusiform nuclei in an eosinophilic matrix characteristic of the Antoni-A pattern of neurilemmoma (Grade I). (B) Histology of third excision biopsy (June 2007) demonstrating the greater and more uniform cellularity, and larger, subtly pleomorphic nuclei of MPNST. (C) Final biopsy (November 2007) demonstrating a dense sheet of pleomorphic nuclei with reduced eosinophilic cytoplasm consistent with an anaplastic soft-tissue sarcoma.

performed via a posterior fossa approach (Fig. 4A). Histology showed morphological transformation to an MPNST (Fig. 5B) with now only focal S100 protein. Within the next 3 months there was a rapid and aggressive recurrence of the tumor with brainstem compression (Fig. 4B). Further surgery was performed to decompress the brainstem. Histology revealed further de-differentiation to an anaplastic soft-tissue sarcoma devoid of S100 protein and other tissue-specific markers (Fig. 5C). While awaiting radiotherapy, the tumor recurred further within 4 weeks (Fig. 4C) and the patient died. The patient had no features of NF2.

DISCUSSION

Acoustic neuromas or vestibular schwannomas are benign tumors arising from the eighth cranial nerve. MPNST in the eighth cranial nerve is extremely rare, and the transformation of a benign tumor to a sarcoma like MPNST is equally rare in the absence of underlying neurofibromatosis. Acoustic neuromas very rarely undergo a malignant transformation. In the literature we found 14 (including this one) cases of malignant acoustic neuromas (Tables 1 and 2). In these only six cases had radiotherapy and of these only three actually had histological confirmation of a benign lesion before radiotherapy and then malignant histology after radiotherapy. None of these three (our case included) had neurofibromatosis. Three other cases had histological proof of a malignant tumor after radiosurgery, but none had preradiotherapy histology at all; of these two were positive for neurofibromatosis. Malignant acoustic neuromas also have been reported in the absence of radiosurgery; five cases with malignant histology from the start, and two cases with confirmed benign histology that underwent malignant transformation in the absence of radiosurgery.

Risk of Malignancy after Gamma Knife Stereotactic Radiosurgery

Despite the widespread use of radiosurgery, the risk of radiation-induced malignancy after this modality is largely unknown. A retrospective cohort study from Sheffield looked at nearly 5000 patients with a 30,000 patient-years of follow-up.[2] No excess incidence of intracranial malignancy was detected; in fact only one case of an astrocytoma was detected after GKS for a cavernoma. This series included 856 cases of vestibular schwannoma but the follow-up here was only 3.8 years. Comparing this with the latency period to postirradiation tumor formation in the cohort of children treated for tinea capitis in Israel (1948–1960), we find that it is 14 years for gliomas and 21 years for meningiomas.

Cranial Irradiation and Sarcoma Development

Sarcoma development after cranial irradiation is rare but potentially fatal. Chang et al (1995) reported seven cases who after radiotherapy (1600–6000 cGy) developed sarcomas within the irradiated field.[5] The median time from radiation to sarcoma development was 8 (range 4 to 15) years and the median survival from diagnosis was 19 months. In our case the time interval was 10 years and the survival from final diagnosis was 4 months. The incidence of radiation-induced MPNSTs ranges from 5.5 to 11%.[6] Although the presence of a new lesion after radiotherapy for primary brain pathology should point to recurrence as the most likely diagnosis, the differential of sarcoma development should be considered.

A potential mechanism is radiation-induced mutagenesis. The observed predisposition for radiation-related tumors in Li–Fraumeni syndrome, where a mutation in the p53 tumor suppressor gene is present on one chromosome, may suggest that a mutation on the other chromosome may be a step in carcinogenesis.[7] In fact, both radiation-induced sarcomas and sporadic ones have been shown to have p53 mutations.[8,9] Indeed, one irradiated acoustic neuroma that did malignantly transform had a mutation in p53.[3] Another hypothesis concerns potential effects on the microenvironment that may lead to preferential proliferation of preexisting malignant cells.

Cranial Irradiation and Molecular Biology of Acoustic Neuromas

Acoustic neuromas form when the tumor suppressor gene NF2 is inactivated. NF2 produces the protein *merlin* whose loss alters schwann cell regulation leading to tumor formation.[10] Only 60% of tumors carry mutations or deletions of NF2 gene. This suggests a heterogeneity in pathogenesis and therefore potentially also in growth rate and radiation sensitivity. Apart from the known effects of radiation on p53, Lee et al performed a microsatellite analysis of recurrent acoustic neuromas that underwent stereotactic gamma knife radiosurgery.[11] They found 20/26 of sporadic non-irradiated acoustic neuromas had an allelic loss of 22q, whereas none of the four irradiated recurrent tumors demonstrated loss of heterozygosity on chromosome 22q. Neither group had any allelic loss in chromosome 10, where deletions have previously been observed with radiation effects. However, when screening for *merlin*, none of the irradiated group expressed the protein. This suggests an alternative mechanism of NF2 inactivation that may correlate with radiosensitivity in acoustic neuromas.

Proliferative Activity in Acoustic Neuromas

Different growth rates have been observed between sporadic and neurofibromatosis-related tumors and

Table 1 Clinicopathological Characteristics of All Previously Published Cases of Malignant Acoustic Neuromas/Vestibular Schwannomas

Reference	Age/ Sex	NF2	Symptom Duration	Initial Histology	Radiation Dose	Subsequent Operation	Final Histology	Outcome
Current case	27/M	No	10 months deafness, facial numbness, imbalance	Vestibular schwannoma	GKS 15 Gy to 50% isocontour and 9 Gy to brainstem. 6 months later also had GKS to ipsilateral parietal AVM	2 years (regrowth) 10 years GTR (due to gross enlargement) 3 months later GTR (due to full recurrence)	Vestibular schwannoma MPNST Further de-differentiation to anaplastic soft-tissue sarcoma	Died within 6 months of representing 10 years from initial presentation. While awaiting radiotherapy, tumor had recurred within 4 weeks
Bari et al[13]	28/F	Yes	2 years deafness and facial numbness	No	1500 cGy GKS	GTR 4 years later	Malignant transformation suggested by some areas of S100 protein	Died that year
McLean et al[14]	75/M	No	1 month deafness, facial palsy	Vestibular schwannoma	No radiation	1 year later	Malignant change	Died within that year
Comey et al[15]	50/M	No	1 year decreased hearing	No	14.4 Gy GKS	5 years later and again 4 months after that	Triton	Died 1 year later
Hanabusa et al[16]	57/F	No	1 year decreased hearing	Vestibular schwannoma	15 Gy GKS 5 years post-op	6 months after GKS and further GKS to residuum. 2 further palliative ops	2nd op's histology was ''Atypical'' ascribed to GKS. Final showed malignant transformation	Died 6.5 years after initial treatment
Kudo et al[17]	54/M	No	Hearing loss 5 yrs	Subtotal resection 1981: MPNST	No	2 more ops 1982	MPNST	
Shin et al[18]	26/F	No	Hearing loss of unspecified duration	Vestibular schwannoma	17 Gy GKS 1 month post-op	6 years later	MPNST	Died 10 months later
Gruber et al[19]	61/F	No	Unilateral sudden deafness and imbalance on background of known symmetrical hearing loss	Low grade malignant Vestibular schwannoma	No	No	N/A	2 years follow-up with no recurrence
Thomsen et al[20]	19/F	Yes	Bilateral hearing loss for 18 months	GTR on left: Vestibular schwannoma. GKS to Right	12 Gy only to right (non operated) side	6 years later	Anaplastic tumor on the right	Died 8 years after initial tx
Mrak et al[21]	40/M	No	2 months facial numbness and unsteadiness	Malignant acoustic schwannoma	Not until after 2nd op	10 months after 1st op, followed by GKS 11 months after that	As before	Housebound at 39 months from presentation
Matsumoto et al[22]	54/M	No	Deafness and tinnitus for 5 years, with 2 normal CTs, then facial tingling	MPNST	No	2 further ops within 3 months	MPNST	Died at 4 months
Gonzalez et al[23]	43/F	No	1 month N+V 2 weeks unsteadiness, deafness, facial weakness	Malignant Vestibular schwannoma	After 2nd op	2nd op for GTR, then SRS 5040cGY	As before	Recurrence at 5 months and contralateral lesion. Died 8 months
Wilkinson et al[24]	53/M	No	Not stated	Vestibular schwannoma	Yes ?dose	Debulking 7 years later	MPNST	?
Son et al[25]	33/F	No	1 year vertigo and hearing loss	Vestibular schwannoma	No	Recurrence at 2 months with further surgery	Malignant vestibular schwannoma	Refused radiotherapy. Recurred 1 month after 2nd op and had 3rd op. Stable at time of writing 1 year later

Table 2 The Relation of Previously Published Malignant Acoustic Neuromas/Vestibular Schwannomas to Neurofibromatosis Type 2 and the Presence of Benign and Malignant Histology in Relation to Radiosurgery

	No History of NF2	History of NF2
Initial benign histology with subsequent radiation and final malignant transformation	3	0
No initial histology with radiation as initial treatment and final malignant histology	1 (but Triton tumor)	2
Malignant histology de novo	5	0
Benign initial histology with no radiation and malignant transformation	2	0

between solid and cystic schwannomas. We reviewed the original histology from 1997 in our case and confirmed no features of atypia existed in the diagnosis of benign vestibular schwannoma. There is no currently uniform set of histological criteria for low-grade malignant acoustic neuromas; one of the five non-irradiated malignant acoustic neuromas had such a label. Light et al addressed this issue by examining "atypical" and "low-grade malignant" vestibular schwannomas.[12] Mean follow-up was only 3.5 years, yet 0/8 recurrences were observed in the former group and 2/6 in the latter. Neither group had distant metastases nor aggressive local invasion, although MIB-1 labeling indices were significantly higher in both groups than the control. This may suggest a different clinical behavior than typical benign vestibular schwannomas and perhaps calls for a reclassification. It does, though, also suggest that those typical vestibular schwannomas that became malignant after radiotherapy were of a different subtype and may not otherwise have been inclined to transform.

CONCLUSION

Malignant transformation of a benign non-NF2-associated acoustic neuroma does exist. Although it is impossible to draw epidemiological conclusions from case reports, gamma knife is generally regarded as safe and the risk of malignant transformation, with or without radiosurgery, is very low. Long-term follow-up data will become available with time, yet the increase in patient numbers treated primarily with this modality suggests caution should be exercised in its use in young people, and patients should be informed of this rare but potentially serious complication.

NOTES

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