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Case Report

Malignant transformation of vestibular schwannoma after radiation therapy ☆,☆☆

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ABSTRACT

Stereotactic radiosurgery (SRS) is an effective treatment for vestibular schwannomas, offering high rates of tumor control and low neurological risks. Long-term complications of SRS are not fully understood, with several cases of malignant transformation reported in the literature. We report the case of a 50-year-old female with no prior history of neurofibromatosis who presented in 2013 with MRI evidence of a benign vestibular schwannoma. Despite treatment with CyberKnife SRS, she presented 6 years later with new onset neurologic symptoms. Further investigation showed stable lesion size with increasing vasogenic edema and a new area of enhancement in the brainstem, suspicious for malignant transformation. Subsequent treatment with partial craniectomy and histopathologic analysis was consistent with a malignant peripheral nerve sheath tumor diagnosis. Our case adds to a series of 24 similar cases in the literature, details of which have been summarized in our study. Overall, findings support the need for lifelong surveillance following SRS treatment of benign vestibular schwannomas. Patients should be educated on the potential risk of this complication, and clinicians must maintain a high level of suspicion for potential radiation-induced malignancy during the patient's clinical course.

Abbreviations: VS, vestibular schwannoma; SRS, stereotactic radiosurgery; MPNST, malignant peripheral nerve sheath tumor; MRI, magnetic resonance imaging.

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Background

Vestibular schwannomas (VSs) are known to be the most common benign tumor of the cerebellopontine angle (CPA) in adults [1,2]. Typically, these tumors carry an excellent prognosis, with malignant transformation being rare and primarily associated with neurofibromatosis [3]. Management options include observation, microsurgical resection, and radiosurgery [1,4,5]. Stereotactic radiosurgery (SRS) is useful for VSs <3 cm, offering effective tumor control with minimal neurological risks [4–6].

With SRS becoming the primary treatment of choice for small VSs, recognizing and understanding potential risks is essential. In this article, we present the case of a malignant peripheral nerve sheath tumor (MPNST) that emerged 6 years after treating a benign VS with SRS, along with a literature review and discussion regarding this relatively underrecognized risk.

Case presentation

A 50-year-old female with no prior history of neurofibromatosis, presented with progressive right-sided hearing loss, vertigo, and nausea. Initial magnetic resonance imaging (MRI) revealed a right CPA lesion consistent with a benign VS (Fig. 1). Managed conservatively, annual follow-up MRI showed mild tumor growth, leading to treatment with CyberKnife SRS (1800 cGy in 3 fractions).

After 6 years of stability, she developed right temporal pain, facial numbness, dysphagia, and diplopia. MRI showed increased vasogenic edema and a new brainstem enhancement adjacent to the tumor, suggesting malignant transformation (Fig. 2). She underwent partial surgical resection with histopathologic confirmation of a schwannoma with focal malignant transformation consistent with MPNST. The tumor showed areas of typical grade 1 schwannoma alternating with highly cellular, sarcoma-like areas (Figs. 3 and 4).

Adjuvant radiation was administered 6 months after surgery. Sixteen months later, the patient experienced worsening symptoms, including complete right-sided hearing loss, episodes of right facial pain, and severe dysphagia. Imaging revealed stable posttreatment and postsurgical changes without evidence of further tumor progression. No further surgical treatment was pursued, and the patient was managed symptomatically. Unfortunately, she passed away the following year due to respiratory complications associated with aspiration.

Discussion and conclusions

Radiation-induced malignant transformation of VSs represents a rare yet significant complication following SRS. Radiosurgery has emerged as a minimally invasive approach for smaller VSs, offering high tumor control and minimal side effects [4]. However, long-term effects are unclear, with increasing reports of radiation-induced malignancies [7–9]. Our case adds to a series of 24 such cases in the literature, primarily involving MPNSTs in patients with no prior history of neurofibromatosis (Table 1) [8–28]. Including our case, most patients were females, averaging 54 years at the time of malignant transformation. Marginal doses ranged from 10-17 Gy, and maximal doses ranged from 20-34 Gy. 20 (80.0%) patients underwent Gamma Knife radiosurgery, 2 (8.0%) were treated with CyberKnife SRS, and 1 (4.0%) received Linear Accelerator SRS. In 2 (8.0%) cases, the employed radiosurgery technology was not specified. The mean time to malignant transformation was 6 years, with MPNSTs constituting the majority (19 cases, 76.0%), while 6 (24.0%) cases evidenced transformation into high-grade sarcomas. Prognosis was poor with survival ranging from 1-24 months.

Traditionally, the Cahan criteria are pivotal in categorizing a tumor as radiation-induced [29,30]. These criteria entail: 1) acquisition of pretreatment pathology confirming benign tumor diagnosis, 2) manifestation of malignancy within the radiation field, 3) a sufficient interval between radiation exposure and malignancy onset (>5 years), and 4) posttreatment pathology verifying malignant diagnosis [29,30]. From the 24 cases identified, 16 had a confirmed histologic VS diagnosis before SRS. Conversely, 8 cases lacked initial pathology but were classified as benign VSs owing to discernible radiologic features (Table 1). Despite these cases not fully aligning with the Cahan criteria, the potential of a radiation-induced malignancy persists. This is accentuated by factors such as 1) the high sensitivity (96%-100%) and specificity (88%-93%) of imaging in diagnosing VSs, 2) the consistent long latency periods of at least 5 years in all 8 cases, and 3) 3 of the 8 cases confirming benign tumor presence prior to malignancy onset through post-SRS pathology [31].

In our case, pre-SRS pathology was not obtained. However, initial imaging was compatible with a benign VS, and the patient's tumor remained stable for 6 years on annual follow-up MRI, rendering the existence of a small pre-irradiation malignant component unlikely. Postsurgical pathology revealed malignant cells amidst a benign VS, supporting the theory of malignancy originating from a benign tumor.

The mechanism by which radiation may induce malignant transformation is largely unknown [32]. Despite SRS delivering high radiation doses to confined tissue volumes, theoretically favoring cytotoxicity over mutagenicity, certain cases have expressed well-established radiation-induced alterations such as P53 mutations or H3K27 trimethylation loss in post-SRS tumor tissue [10,26]. Differences in clinical attributes have also been noted between *de novo* and radiation-induced MPNSTs, with the latter exhibiting a worse prognosis [32].

In conclusion, our case underscores the need for lifelong surveillance following SRS treatment of benign VSs. Familiarity with the clinical and imaging characteristics of MPNSTs is critical, as clinicians must be vigilant to potential malignant changes during the patient's clinical course. Adequate patient counselling regarding the potential for malignant transformation prior to SRS is paramount, especially for those at higher risk, like younger individuals and patients with neurofibromatosis [1].

Table 1 – Cases of radiation-induced malignant transformations of VSs following treatment with SRS in patients without neurofibromatosis.

Investigators	Age[a] / Sex	Initial pathology	Tumor treatment[c]	Radiation dose	Latency (Mo)[b]	Final pathology	Survival
Hosmann et al. 2024 [7]	50, F	VS	S, S, GKS, **S**	13 Gy 50%	66	High-grade spindle cell sarcoma	NR
Behling et al. 2022 [10]	41, F	None	GKS, S, GKS, S, Biopsy, **S**	12.0 Gy 50% 12.5 Gy 60% (maximum 20.8 Gy)	N/A	MPNST	4 mo
De Jesus et al. 2021 [8]	56, M	VS	S, GKS, **S** x 2	12.0 Gy 50% (maximum 24 Gy)	108	MPNST	Palliative, further f/u NR
Li et al. 2021 [9]	53, F	VS	S, S, GKS, **S**	NR	12	MPNST	6 mo
Li et al. 2021 [9]	67, F	VS	S, GKS, **S**, GKS, S	NR	26	MPNST	Reirradiation, further f/u NR
Li et al. 2021 [9]	32, F	VS	S, GKS, GKS, **S**	NR	20	MPNST	NR
Boucher et al. 2020 [11]	66, F	None	GKS, **S**	12.5 Gy 50% (maximum 25 Gy)	204	High-grade sarcoma	7 mo
Haq et al. 2019 [12]	64, M	VS	S, GKS, S, **S**, RT	10.0 Gy 50% (maximum 20 Gy)	122	MPNST	Reirradiation, further f/u NR
Peker et al. 2019 [13]	40, F	VS	S, CKS, **S**, S	NR	NR	MPNST	NR
Tish et al. 2019 [14]	65, F	None	SRS, **S**, RT, RT	12.0 Gy 50%	~132	MTT	10 mo
Wolf et al. 2019 [15]	NR	VS	S, GKS, **S**	12.0 Gy (maximum 24.3 Gy)	104	MPNST	~24 mo
Frischer et al. 2018 [16]	NR	None	GKS, S, **S**	13.0 Gy 50% (maximum 26 Gy)	96	MPNST	9 mo
Se et al. 2017 [17]	55, F	None	GKS, **S**, CT	12.5 Gy 50%	72	Sarcoma	NR
Seferis et al. 2014 [18]	54, F	VS	S, GKS, **S**, GKS	12.0 Gy 45% (maximum 26.7 Gy)	66	MPNST	Reirradiation, further f/u NR
Yanamadala et al. 2013 [19]	51, F	VS	S, GKS, S, **S**, S, S, CT	14.0 Gy 50% (maximum 28 Gy)	59	MPNST	11 mo
Puataweepong et al. 2012 [20]	41, F	VS	S x2, Linac, **S**, RT	30.0 Gy in 6 fractions at 80% isodose line	72	MPNST	2 mo
Schmitt et al. 2011 [21]	59, M	None	GKS, **S**, CT	12.0 Gy (maximum 30 Gy)	90	UHGPS	7 mo
Akamatsu et al. 2010 [22]	81, F	VS	S, S, GKS, **S**, RT	12.0 Gy (maximum 24.4 Gy)	96	MPNST	NR
Demetriades et al. 2010 [23]	37, M	VS	S, GKS, S, **S**, S	15.0 Gy 50% (maximum 30 Gy)	120	MPNST	6 mo
Yang et al. 2010 [24]	74, M	VS	S, SRS, **S**	12.5 Gy 80%	72	High-grade undifferentiated sarcoma	~1 mo
Hasegawa et al. 2005 [25]	61, F	None	GKS, S x5	12.7 Gy	66	MPNST	13 mo
Shin et al. 2002 [26]	32, F	VS	S, GKS, **S**, S, CT	17.0 Gy 50%	72	Malignant schwannoma	10 mo
Hanabusa et al. 2001 [27]	55, F	VS	S, GKS, **S**, GKS, S x2	15.0 Gy 50% (maximum 30 Gy) 14.0 Gy 50% (maximum 28 Gy)	6	Sarcomatous change	Reirradiation, death within 13 mo
Comey et al. 1998 [28]	49, M	None	GKS, **S**, S, FRT	14.36 Gy 40% (maximum 34 Gy)	~60	MTT	12 mo

CKS, CyberKnife radiosurgery; CT, chemotherapy; f/u, follow-up; GKS, Gamma Knife radiosurgery; Gy, Gray; MPNST, malignant peripheral nerve sheath tumor; MTT, malignant triton tumor; NR, not reported; RT, radiotherapy; S, surgery; UHGPS, undifferentiated high-grade pleomorphic sarcoma; VS, vestibular schwannoma.

[a] Age is defined as the age at malignant transformation.

[b] Latency is defined as the period between radiation treatment and malignant transformation diagnosis.

[c] Bolded treatment indicates the time at malignant transformation.

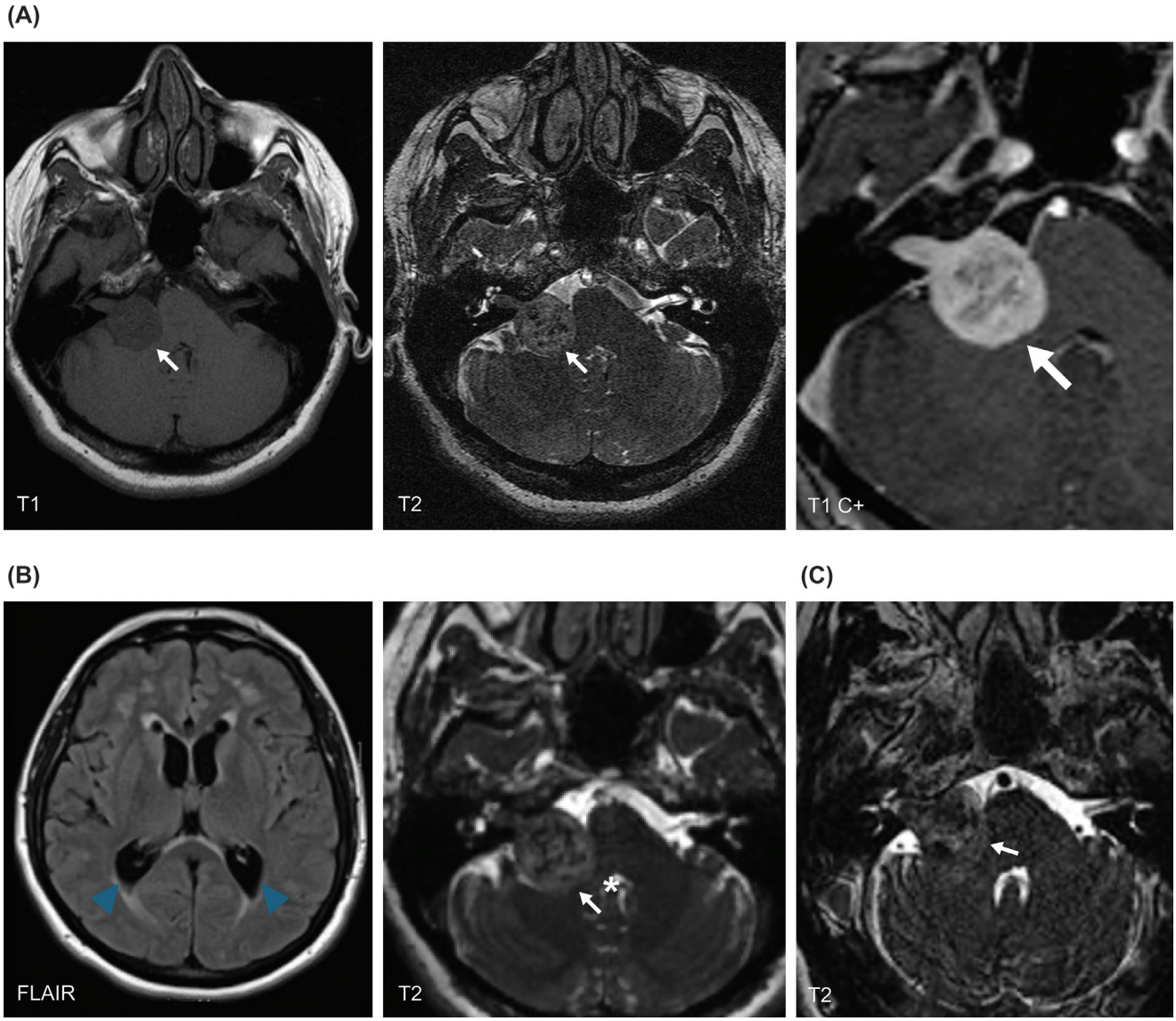

Fig. 1 – (A) Initial MRI showed a right CPA lesion *(white arrows)* with low T1 signal, heterogenous high T2 signal and diffuse enhancement extending into the *porus acusticus*, occupying the right internal auditory canal. (B) Pre-SRS imaging showed increased lesion size *(white arrow)* with mass effect over the brainstem, causing effacement of the fourth ventricle *(white asterisk)* and mild supratentorial hydrocephalus *(blue arrowheads show enlargement of the trigones of the lateral ventricles and surrounding transependymal edema, features consistent with obstructive hydrocephalus)*. (C) MRI 5 years post-SRS confirmed tumor stability *(white arrow)*.

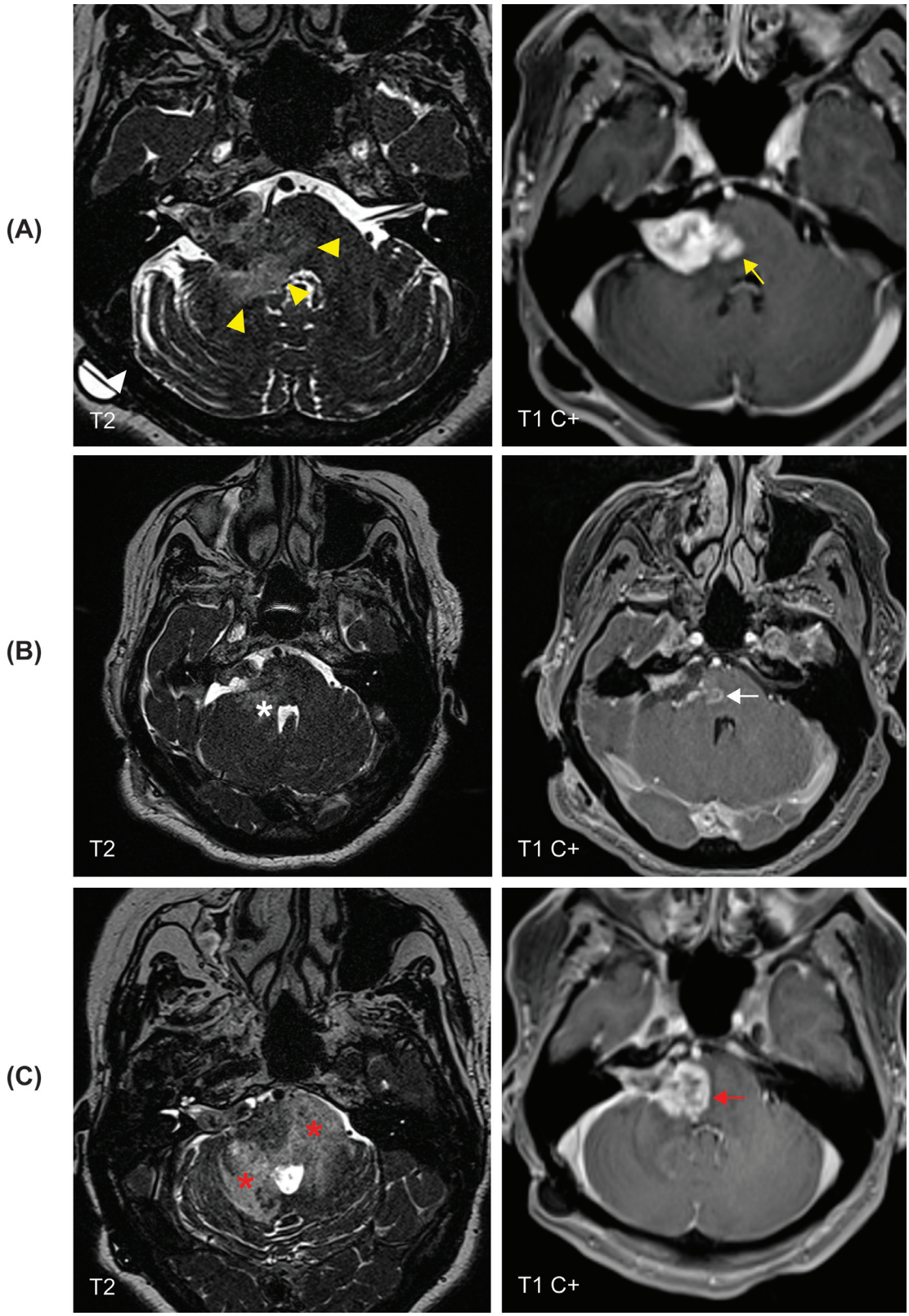

Fig. 2 – (A) MRI 6 years post-SRS showed changes in tumor morphology with increasing vasogenic edema *(yellow arrowheads)* and a new area of enhancement extending from the medial aspect of the tumor to the brainstem *(yellow arrow)*. (B) Imaging post right suboccipital craniectomy confirmed the presence of a residual lesion with persistent enhancement in the right hemi pons *(white arrow)* and abnormal signal in the *brachium pontis (white asterisk)*. (C) Following the completion of adjuvant radiation, imaging showed an increase in residual lesion size *(red arrow)* and worsening signal abnormality in the adjacent brainstem and *brachium pontis (red asterisks)* possibly reflecting treatment-related changes or disease progression.

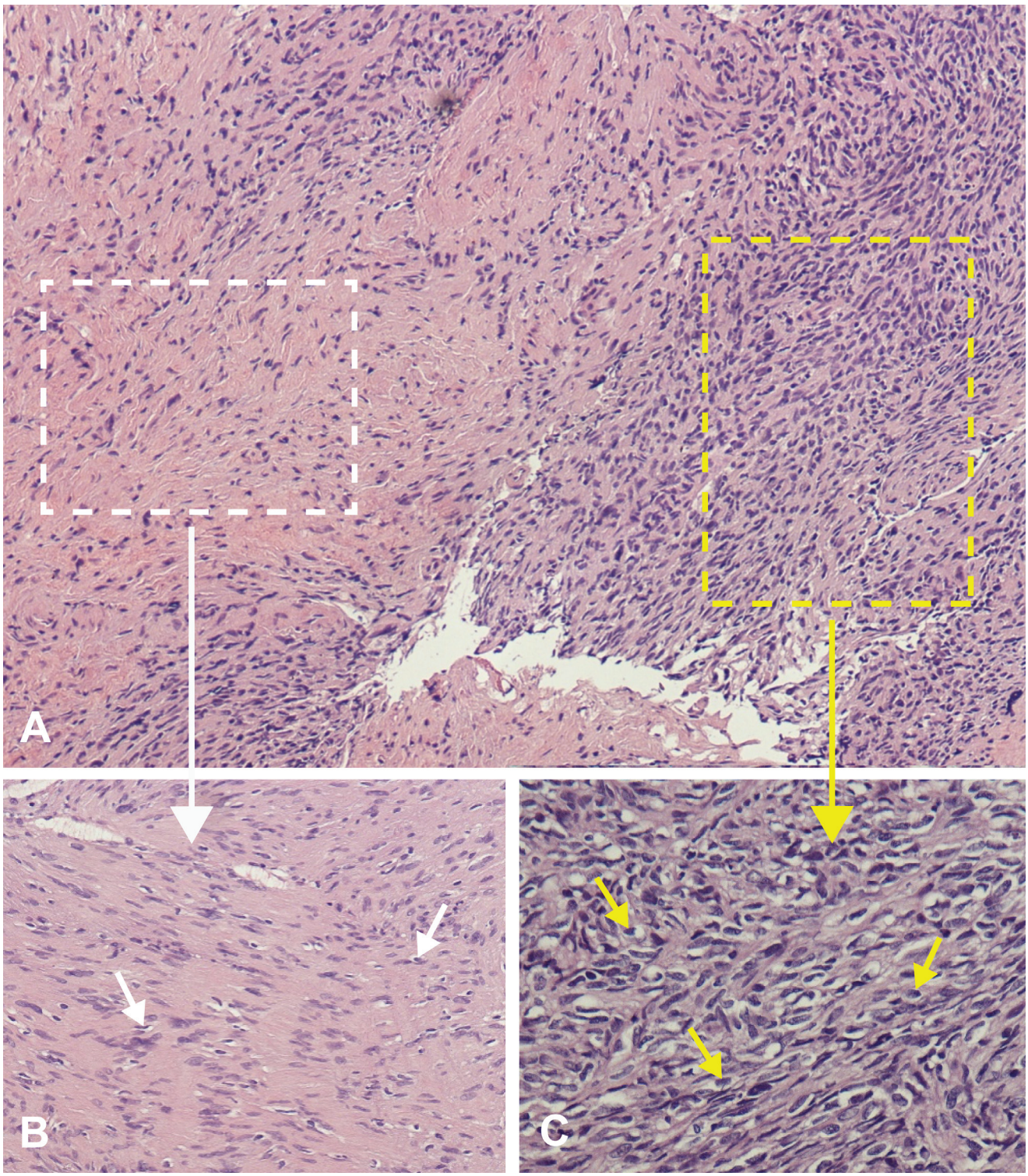

Fig. 3 – (A) Immunohistochemical staining showed a spindle biphasic appearance, with one part showing moderate cellularity on a fibrous background, consistent with a schwannoma (*white*). The other segment displayed notable cellular proliferation (*yellow*). (B) Magnification of the hypocellular area (*white arrows*) with myxoid stroma and hyalinization. (C) Magnification of the highly cellular area shows fascicles of mitotically active spindle cells with wavy, hyperchromatic nuclei (*yellow arrows*).

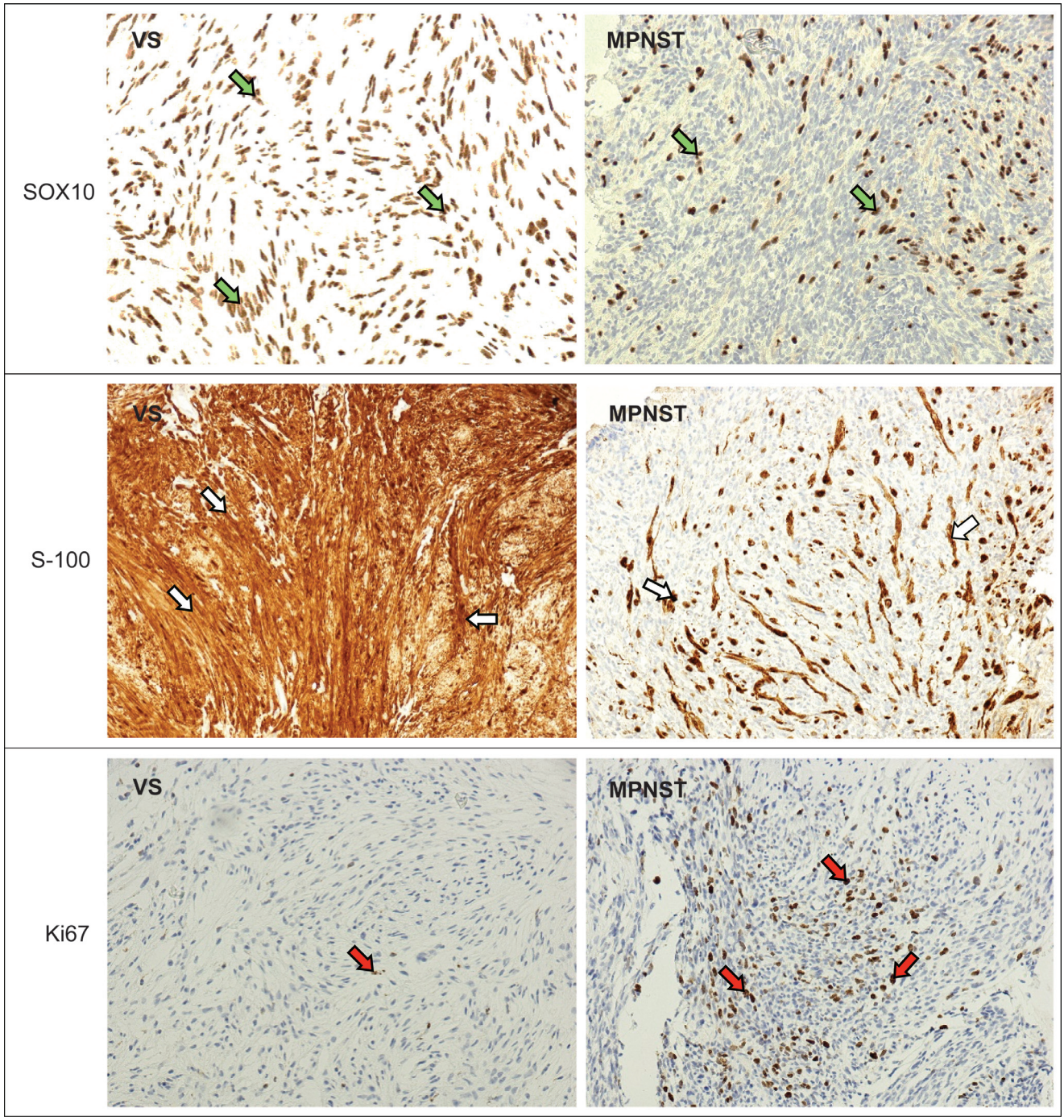

Fig. 4 – (A) Immunohistochemical staining showed diffuse SOX10 positivity in the schwannoma area, while more cellular regions lacked staining *(green arrows)*. (B) Strong expression of the S-100 marker in the schwannoma area while the MPNST stained S-100 positive only focally *(white arrows)*. (C) Increased Ki67 labelling in the MPNST *(red arrows)*.

Authors' contributions

All authors contributed equally to the writing and conduct of this study.

Patient consent

We hereby confirm that authorization for the publication of this case has been obtained from the Ottawa Hospital Research Institute and Ottawa Health Science Network Research Ethics Board (OHSN-REB). No personal identifiable information, beyond what is essential for the educational and scientific purpose, is included in this publication. All efforts to ensure patient anonymity have been met, although complete anonymity cannot be guaranteed. The signed consent forms are retained in our records.

REFERENCES

[1] Carlson ML, Link MJ. Vestibular Schwannomas. N Engl J Med 2021;384(14):1335–48.

[2] Babu R, Sharma R, Bagley JH, Hatef J, Friedman AH, Adamsons C. Vestibular schwannomas in the modern era: epidemiology, treatment trends, and disparities in management: Clinical article. J Neurosurg 2013;119(1):121–30.

[3] Maducdoc MM, Ghavami Y, Linskey E, Djalilian R. Evaluation of Reported Malignant Transformation of Vestibular Schwannoma: De Novo and After Stereotactic Radiosurgery or Surgery. Vol. 36, Otology & Neurotology. Otology & Neurotology, Inc; 1301.

[4] Goldbrunner R, Weller M, Regis J, Lund-Johansen M, Stavrinou P, Reuss D, et al. Eano guideline on the diagnosis and treatment of vestibular schwannoma. Neuro Oncol 2020;22(1):31–45.

[5] Germano IM, Sheehan J, Parish J, Atkins T, Asher A, Hadjipanayis CG, et al. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of radiosurgery and radiation therapy in the management of patients with vestibular schwannomas. In: Clinical Neurosurgery. Oxford University Press; 2018. p. E49–51.

[6] Breivik CN, Nilsen RM, Myrseth E, Pedersen PH, Varughese JK, Chaudhry AA, et al. Conservative management or gamma knife radiosurgery for vestibular schwannoma: tumor growth, symptoms, and quality of life. Neurosurgery 2013;73(1):48–56.

[7] Hossmann A, Kamdar V, Misra BK. Malignant transformation of vestibular schwannoma following radiosurgery – a case report and review of the literature. Acta Neurochir (Wien) 2024;166(1):52.

[8] De Jesus O, Sánchez Jiménez JG, Santiago Quiñones G, Vélez R. Malignant peripheral nerve sheath tumor transformation of histological benign vestibular schwannoma after stereotactic radiosurgery in patients without neurofibromatosis. BMJ Case Rep 2021;14(11):e246445.

[9] Li J, Wang Q, Zhang M, Zhang G, Zhang S, Hui X. Malignant transformation in vestibular schwannoma: clinical study with survival analysis. Front Oncol 2021;11:655260.

[10] Behling F, Bersali I, Santacroce A, Hempel J, Kandilaris K, Schittenhelm J, et al.. Transition of a vestibular schwannoma to a malignant peripheral nerve sheath tumor with loss of H3K27 trimethylation after radiosurgery—a case report and review of the literature, 45. Neurosurgical Review. Springer Science and Business Media Deutschland GmbH; 2022. p. 915–22.

[11] Boucher AB, Mendoza P, Neill SG, Eaton B, Olson JJ. High-grade sarcoma arising within a previously irradiated vestibular schwannoma: a case report and literature review. In: World Neurosurgery. Elsevier Inc.; 2020. p. 99–105.

[12] Haq IBI, Goto T, Kawashima T, Yamanaka K, Osawa M, Ohata K, et al. Malignant transformation of a vestibular schwannoma to malignant peripheral nerve sheath tumor 10 years after Gamma Knife Surgery: Case report. Interdiscip Neurosurg 2019;18:100529.

[13] Peker HO, Gok H, Altay T. Malignant transformation of vestibular schwannoma after stereotactic radiosurgery. World Neurosurg 2019;124:81–3.

[14] Tish S, Ross L, Habboub G, Roser F, Recinos PF. Malignant triton tumor diagnosed twelve years after radiosurgically treated vestibular schwannoma. Clin Neurol Neurosurg 2019:183.

[15] Wolf A, Naylor K, Tam M, Habibi A, Novotny J, Liščák R, et al. Risk of radiation-associated intracranial malignancy after stereotactic radiosurgery: a retrospective, multicentre, cohort study. Lancet Oncol 2019;20(1):159–64.

[16] Frischer JM, Gruber E, Schöffmann V, Ertl A, Höftberger R, Mallouhi A, et al. Long-term outcome after Gamma Knife radiosurgery for acoustic neuroma of all Koos grades: a single-center study. J Neurosurg 2018;130(2):388–97.

[17] Se YB, Kim DG, Park SH, Chung HT. Radiation-induced osteosarcoma after Gamma Knife surgery for vestibular schwannoma: a case report and literature review. Acta Neurochir (Wien) 2017;159(2):385–91.

[18] Seferis C, Torrens M, Paraskevopoulou C, Psichidis G. Malignant transformation in vestibular schwannoma: report of a single case, literature search, and debate. J Neurosurg 2014;121:160–6.

[19] Yanamadala V, Williamson RW, Fusco DJ, Eschbacher J, Weisskopf P, Porter RW. Malignant transformation of a vestibular schwannoma after gamma knife radiosurgery, 79. World Neurosurgery. Elsevier Inc.; 2013. p. 593. Vol.e1-593.e8.

[20] Puataweepong P, Janwityanujit T, Larbcharoensub N, Dhanachai M. Radiation-induced peripheral malignant nerve sheath tumor arising from vestibular schwannoma after linac-based stereotactic radiation therapy: a case report and review of literatures. Case Rep Med 2012;2012:648191.

[21] Schmitt WR, Carlson ML, Giannini C, Driscoll CL, Link MJ. Radiation-induced sarcoma in a large vestibular schwannoma following stereotactic radiosurgery: Case report. Neurosurgery 2011;68(3):E840–6.

[22] Akamatsu Y, Murakami K, Watanabe M, Jokura H, Tominaga T. Malignant peripheral nerve sheath tumor arising from benign vestibular schwannoma treated by gamma knife radiosurgery after two previous surgeries: A case report with surgical and pathological observations, 73. World Neurosurgery. Elsevier Inc.; 2010. p. 751–4.

[23] Demetriades AK, Saunders N, Rose P, Fisher C, Rowe J, Tranter R, et al. Malignant transformation of acoustic neuroma/vestibular schwannoma 10 years after gamma knife stereotactic radiosurgery. Skull Base 2010;20(5):381–7.

[24] Yang T, Rockhill J, Born DE, Sekhar LN. A case of high-grade undifferentiated sarcoma after surgical resection and stereotactic radiosurgery of a vestibular schwannoma. Skull Base 2010;20(3):179–83.

[25] Hasegawa T, Fujitani S, Katsumata S, Kida Y, Yoshimoto M, Koike J. Stereotactic radiosurgery for vestibular schwannomas: analysis of 317 patients followed more than 5 years. Neurosurgery 2005;57(2):257–63.

[26] Shin M, Ueki K, Kurita H, Kirino T. Malignant transformation of a vestibular schwannoma after gamma knife radiosurgery. Lancet 2002;360(9329):309–10.
[27] Hanabusa K, Morikawa A, Murata T, Taki W. Acoustic neuroma with malignant transformation. Case report. J Neurosurg 2001;95(3):518–21.
[28] Comey C, McLaughlin M, Who H, Martinez A, Lunsford L. Death from a malignant cerebellopontine angle triton tumor despite stereotactic radiosurgery. Case report. J Neurosurg 1998;89(4):653–8.
[29] Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone: report of eleven cases. 1948. Cancer 1998;82(1):8–34.
[30] Murray E, Werner D, Greeff E, Taylor D. Postradiation sarcomas: 20 cases and a literature review. Int J Radiat Oncol Biol Phys 1999;45(4):951–61.
[31] Dunn IF, Bi WL, Mukundan S, Delman BN, Parish J, Atkins T, et al. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of imaging in the diagnosis and management of patients with vestibular schwannomas. In: Clinical Neurosurgery. Oxford University Press; 2018. p. E32–4.
[32] Yamanaka R, Hayano A. Radiation-induced malignant peripheral nerve sheath tumors: a systematic review. In: World Neurosurgery, 105. Elsevier Inc.; 2017. p. 961–70. e8.