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CLINICAL STUDY

Intracranial melanotic schwannomas: a rare variant with unusual adherent features

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Abstract Intracranial melanotic schwannomas (*IMSch*) are extremely rare nerve sheath tumors with features of Schwann cells that produce melanin. After a thorough review of the available literature since 1967, we report not only the 20th case of *IMSch* but a comprehensive modern-era analysis of radiographic and histological key-points to be considered when diagnosing and treating patients with this rare known entity. This is the case of a 43 years-old woman who presented with severe headaches 9 years ago (2008). At that time, MRI of the brain showed a 1.5 × 1.4 cm lesion at the level of the left cerebellar peduncle without any evidence of edema, mass effect or hydrocephalus. Given that the patient was neurologically intact, a conservative management with serial MRIs was recommended. Patient stopped following up due to the absence of symptoms. Over the course of the past year, patient noted mild left sided hearing loss and facial weakness, as well as some balance instability that progressed over the last 3 months. Given the presentation and progression of these signs and symptoms, a new MRI was performed in which considerable growth of the lesion was identified, measuring 2.5 × 2.8 × 2.6 cm with mass effect on the pons and the inferior fourth ventricle. She underwent a far lateral approach without a C1 hemilaminectomy for the resection of this lesion. Final pathology was consistent with a non-psammomatous melanotic schwannoma (NPMS) with areas of necrosis. Besides this case, only two other cases of *IMSch* with findings of necrosis have been reported in the literature, all of them reporting a subtotal resection. Evaluation of all previously reported cases of *IMSch* shows a male prevalence with a 1.6:1 male to female ratio. *IMSch* is radiographically T2 hypointense and can be differentiated from Schwannomas that are classically T2 hyperintense. In this case, only a subtotal resection was feasible due to the tumor's overwhelming inherent attachment to vital structures such as cranial nerves (CN), brainstem, and vasculature. While *MSch* is considered histologically benign, several factors including localization, surrounding structures, the rate of growth, tumor volume resection and histological necrosis should be considered in determining prognosis and further adjuvant treatment planning.

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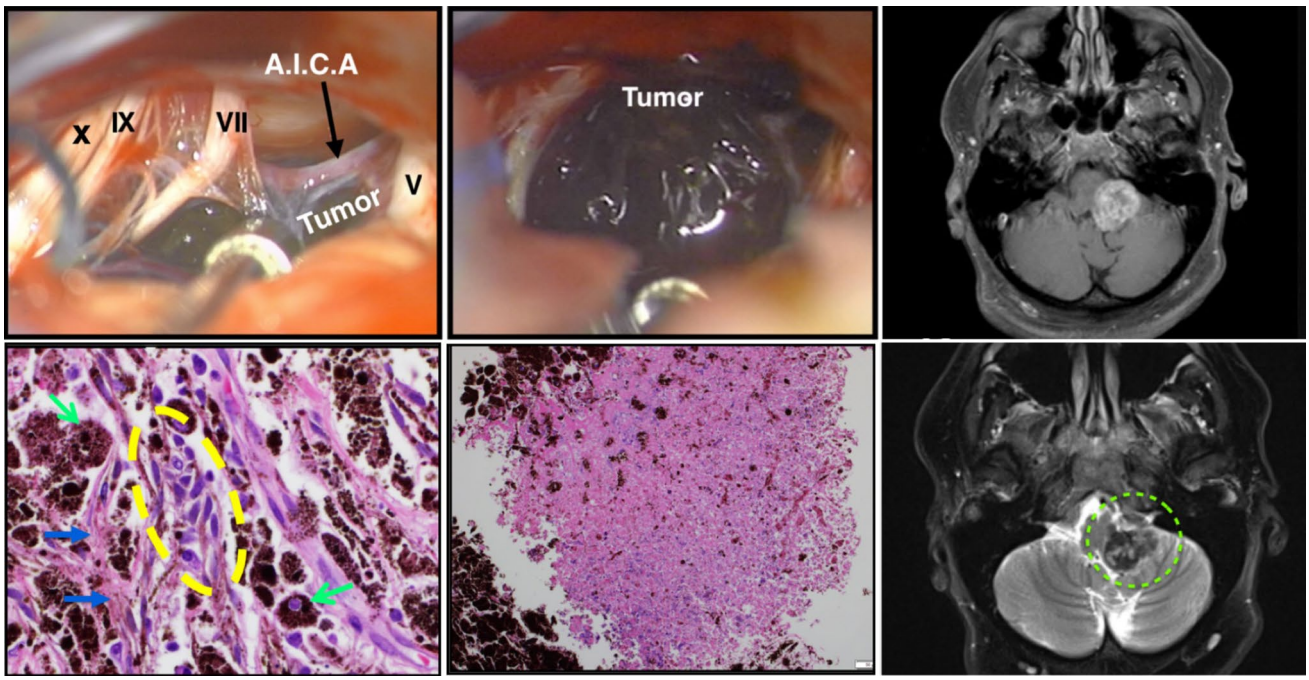
Graphical Abstract



Keywords Melanotic schwannoma · Intracranial · Necrosis · Melanoma · Carney complex

Introduction

Melanotic schwannomas (*MSch*) are extremely rare pigmented neural tumors that are slow growing, encapsulated neoplasms derived from neuroectodermal origin [1–3]. *MSch* represents up to 1% of all nerve sheath tumors and can be found in paraspinal areas, sympathetic ganglion, skin, soft tissues, bone and visceral organs [4–9]. It is thought that this schwannoma variant can synthesize melanin and histologic examination shows both melanocytes and schwann cells [3, 9, 10]. A detailed review of the literature was conducted through PubMed and Google Scholar with the terms: melanotic schwannomas, melanotic tumors, and intracranial location. Only 19 cases of *MSch* with intracranial location were found since 1967, making *IMSch* an extremely rare pathology [9–26]. While *MSch* can be distinguished from typical schwannomas, it is challenging to distinguish *MSch* from malignant melanoma [3, 27, 28]. MS in general is considered a benign tumor, but it can become malignant and even metastasize in patients with familiar syndromes such as Carney complex or neurofibromatosis type II [10, 29, 30]. This manuscript aims to provide a platform with all the reported experiences to generate awareness and a critical thinking among readers for new hypothesis regarding this tumor pathophysiology and treatment.

Illustrative case

This is the case of a 43 years-old woman who presented with severe headaches 9 years ago (2008) and an MRI that showed a heterogeneously enhancing lesion centered within the left middle cerebellar peduncle with mass effect on the left pons measuring $1.5 \times 1.4 \times 1.0$ cm (in the transverse, anteroposterior, and craniocaudal dimensions). The lesion was initially observed with yearly MRIs for the first few years. Given that the lesion was stable with apparent lack of symptoms, the patient stopped following up for almost 7 years. In the last year, she became symptomatic with new balance instability, left sided hearing difficulty, mild left facial paresis and decreased sensation on V2 and V3 distribution. An MRI of the brain demonstrated that the lesion had grown to $2.5 \times 2.8 \times 2.6$ cm (in the transverse, anteroposterior, and craniocaudal dimensions) causing mass effect on the pons and inferior fourth ventricle (Fig. 1). A preoperative CT scan showed a hyperdense lesion arising from the skull base suggesting a vascularized dural based tumor.

Operative details

Preoperative imaging suggested that this was a vascular lesion arising from the skull base with a potential dural attachment. Therefore, in order to safely resect the tumor, we chose a far lateral approach which allowed much better

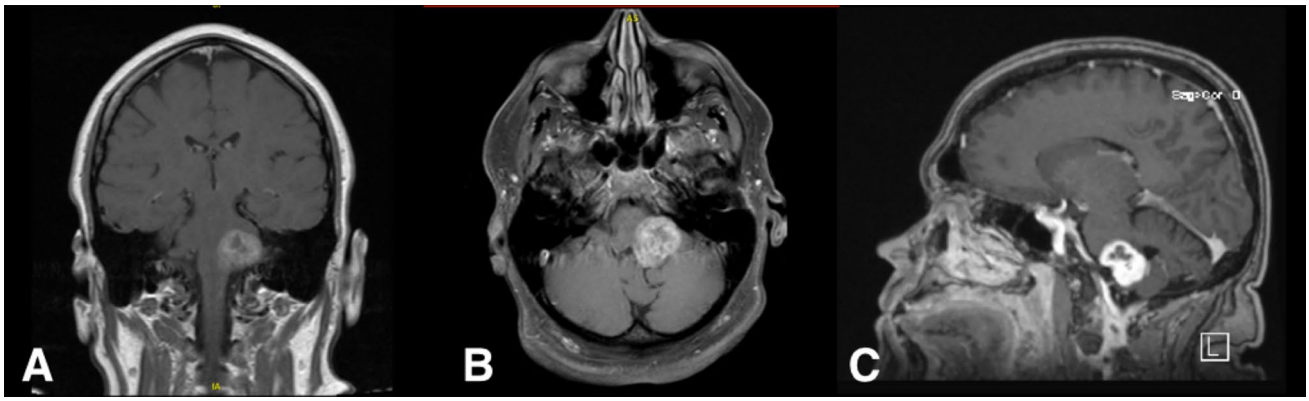


Fig. 1 **a–c** Different sections of an MRI T1 with contrast showing a partially calcified heterogeneously enhancing lesion centered within the left middle cerebellar peduncle with mass effect on the left pons. The lesion measures 2.5 × 2.8 × 2.6 cm (in the transverse, anteroposterior and craniocaudal dimensions). **b, c** Mild compression of the inferior fourth ventricle is identify without hydrocephalus

visualization of the cranial nerves and vasculature in this region. Using a diagonal trajectory, a linear skin incision was made between the asterion and the mastoid tip extending to the spinous process of C2 [31] (Fig. 2). The muscular flap was elevated en bloc with a sub-periosteal dissection performed medially and laterally while protecting the vertebral artery. A paracondylar variation of the Far Lateral approach was performed in the following manner: Three burr holes were placed, one close to the asterion, a second one next to the lower part of sigmoid sinus close to occipital condyle and the last one inferior-lateral to the inion. A suboccipital craniotomy was performed by cutting parallel to the transverse sinus and lateral to sigmoid sinus connecting to the foramen magnum and the occipital condyle. A meticulous drilling around the extracranial aspect of the jugular foramen was carried out using a diamond burr while monitoring for lower cranial nerves. A hemilaminectomy of C1 was not performed in this case. The dura was opened in a cruciate manner reflecting the leaflets toward the sigmoid and transverse sinuses. After opening the dura, the cisterna magna, premedular and cerebellomedular cisterns were dissected using Rhoton micro-instruments. This allowed the brain to relax improving the visualization of the CN V, VII-XI, as well as the tumor (Fig. 4a). The tumor location was

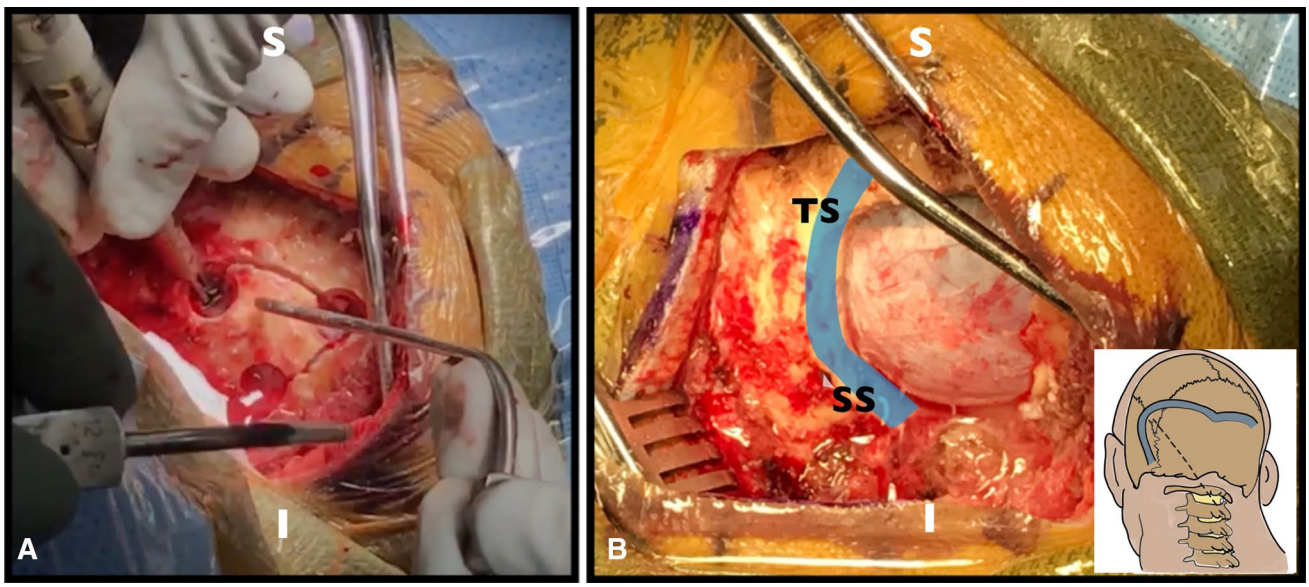


Fig. 2 **a** Three burr holes were placed, one close to the asterion, a second one next to the lower part of sigmoid sinus close to occipital condyle and the last one inferior-lateral to the inion. **b** A suboccipital craniotomy was performed by cutting parallel to the transverse sinus and lateral to sigmoid sinus connecting to the foramen magnum and the occipital condyle. *S* superior, *I* inferior, *TS* transverse sinus, *SS* sigmoid sinus

very complex, and any manipulation of it would cause neuromonitoring changes on CN V and VII. After meticulous and delicate dissection, some parts of the tumor were freed from CN VII and IX, allowing us to resect parts of the tumor located around these structures; however, the majority of the tumor was tenaciously attached to the cranial nerves with no clear plane for dissection (Fig. 4b). The diffuse attachment also made it challenging to discern which CN gave rise to the tumor. A sizable vessel thought to be a branch of the anterior inferior cerebellar artery (A.I.C.A) was visualized within the tumor (Fig. 4c). Any further manipulation of the tumor caused significant firing of CN VII, therefore, we determined that a maximum safe resection was accomplished. At the end the procedure neuromonitoring was stable. The bone flap was secured in place and skin was closed. Post-operatively patient had left House Brackmann grade IV facial deficit with considerable improvement to House Brackmann grade II at her 3-month follow-up visit. The patient is currently undergoing Gamma Knife radiation at 15 Gy.

Pathology result

After careful and extensive study, the final diagnosis was non-psammomatous melanotic schwannoma. It was challenging to make this diagnosis due to dense pigmentation and abundant associated melanophages (Fig. 3d). The cytomorphology of the neoplastic cells, as well as presence of focal collagen IV deposition around cell nests and lack of psammoma bodies supported the diagnosis of non-psammomatous *MSch*. Clinical and histological criteria for malignancy have not yet been clearly formulated for this pathology. Despite the lack of mitotic activity or nuclear anaplasia, the presence of extensive necrosis alludes to a more aggressive tumor behavior. Collagen IV immunohistochemical stain shows a continuous basement membrane around the tumor cells (Fig. 3f). Cells with schwannian differentiation have a continuous basement membrane whereas cells with melanocytic differentiation and histiocytes lack of this feature.

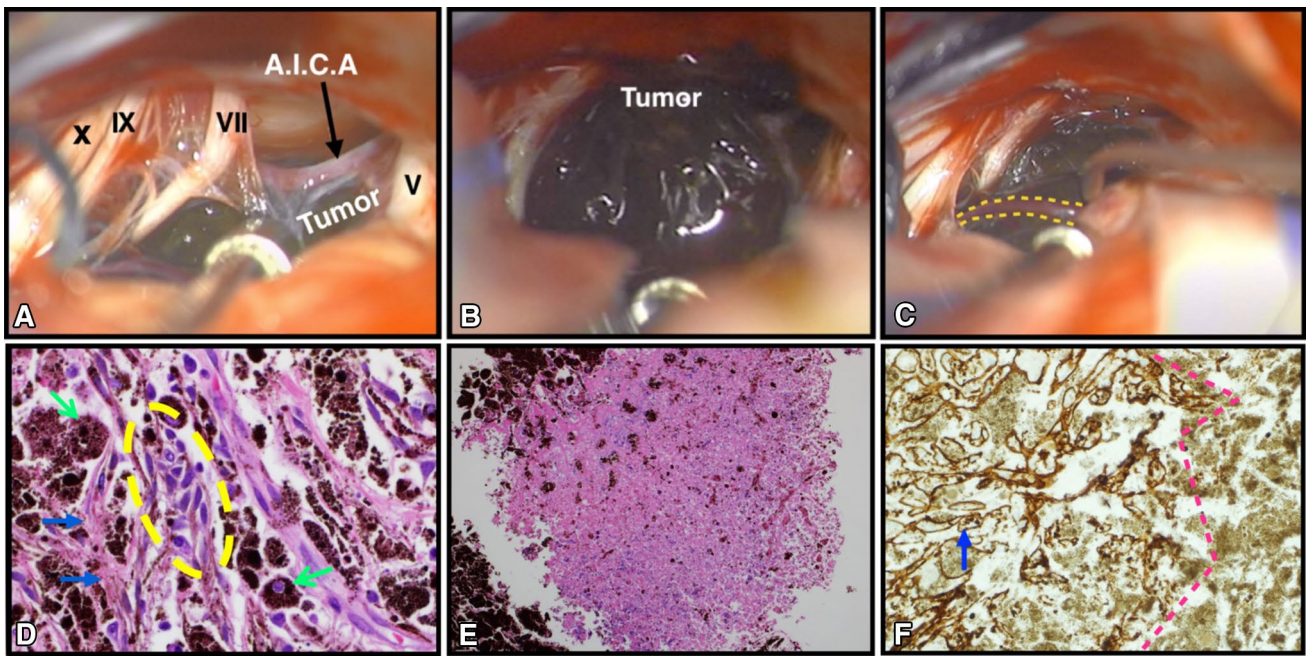


Fig. 3 **a** Cranial nerves V, VII, IX, and X are in close relation with the tumor. **b** A dark tumor can be appreciated after dissection and separation of the cranial nerves. **c** Yellow dashed line showing a branch of A.I.C.A within the tumor. **d** Yellow circle showing a tumor cells nest surrounded by melanophages (green arrows pointing at the melanophages that are macrophages that engulf the melanin pigment released by the tumor cells). The presence of focal collagen IV deposition (blue arrows) around cell nests and lack of psammoma bodies supports the diagnosis of non-psammomatous melanotic schwannoma. **e** Necrosis. **f** (collagen IV immunohistochemical stain) Blue arrow highlights a continuous basement membrane around a tumor cell supporting schwannian differentiation. On the left side of the dashed line, a mixture of cells that have basement membrane staining and ones that don't, representing a mixture of melanophages and cells with schwannian differentiation. On the right hand side of the dashed line are a collection of just melanophages, note the lack of collagen IV staining. *A.I.C.A* anterior inferior cerebellar artery

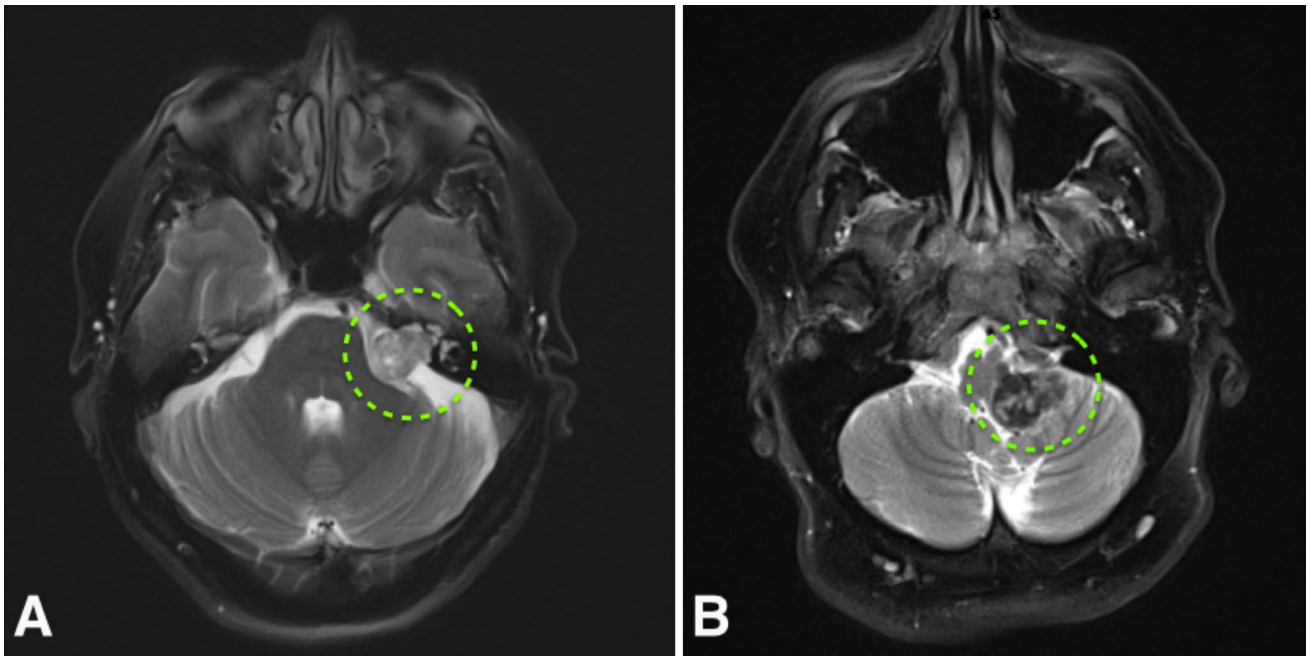


Fig. 4 **a** Schwannoma in left CPA with classical T2 iso-hyperintensity, while **b** shows an intracranial melanotic schwannoma that displays T2 iso-hypointense radiographical features. *CPA* cerebellopontine angle

Discussion

MSchs are a rare variant of schwannoma that accounts for 1% of all nerve sheath tumors that presents in young patients between the fourth and fifth decade [9, 10]. They are mostly found in paraspinal ganglia [4–9]. MSch with an intracranial location are extremely rare presentations and to the best of our knowledge we are reporting the most recent case of intracranial melanotic schwannoma *IMSch*, bringing the total in the world literature to only 20 cases since 1967 [9–26]. Histologically, *MSch* present characteristics of both melanocytes and Schwann cells [3, 26, 32]. Melanocytes and Schwann cells have their embryological origin from the neural crest cells (NC) after emigration form the neural tube (NT). NC cells that migrate dorsolaterally will give rise to melanocytes. NC cells that migrate dorsoventrally will generate Schwann cells progenitors (SCPs) that will later become mature Schwann cells if they stay in contact with nerve fibers. However, detached SCPs from the nerve environment can also indirectly generate melanocytes. This lineage switching from SCPs has been shown to respond to the up/down regulation of FOXD3 being the upregulation favorable to SC differentiation [3, 33, 34]. Their embryological origin, as well as the ability of the Schwann cells to dedifferentiate and re-enter the cell cycle in response to nerve damage [35–37] might be an interesting topic to further explore the etiology of this tumors. Macroscopically, *MSchs* have the appearance of a black tumor that differentiate it from classic schwannomas [1, 3, 5]. Both regular schwannomas and *MSch* are MRI contrast enhancing lesions, however the differential diagnosis of *IMSch* should be considered when a lesion is localized at the CPA with T2 hypointensity. All previously reported *IMSch* cases have been described as T2 isointense to hypointense lesions (Table 1, Fig. 4). The radiographic features of *IMSch* are consistence with other extracranial *MSch* and other tumors that contain melanin such as melanoma [28, 38]. In addition, histologically, *MSch* lacks all the characteristics of schwannoma such as clear cut Antoni A and B features or verocay bodies [7, 39]. A histological differentiation is much more challenging between *MSch* and malignant melanomas, which usually contains psammoma bodies and often exhibits malignant nuclear features such as mitotic figures, necrosis and high KI 67 index [5, 6].

While *MSch* in general is histologically considered a benign tumor that can cause neurological symptoms due to mass effect, it is known to be a more difficult variant to treat than classical schwannomas [9]. After thorough literature search, there were only 26.7% of cases of *MSch* that were resected extra-cranially that recurred locally [4, 7–9]. Vallat-Decovelaere reviewed 77 cases of spinal *MSch* in which 17 patients that were followed > 5 years showed overall recurrence rate of 35.3%, metastasis rate of 29.5%, and mortality rate of 35% [4]. Of the 19 *IMSch* cases, only 6 cases recurred at their last follow-up (Table 1). There was only one case of metastasis to lung despite gross total resection [11]. There was another case where *MSch* was found intracranially and in subsequent imaging a second lesion was

Table 1 Previously reported intracranial melanotic schwannoma cases available in the literature (the present case has been added to this table)

Author	Age	Sex	Location	MRI T2	Resection	Necrosis	Adjuvant treatment	Recurrence
Dastur et al. 1967 [15]	34	M	Acoustic nerve	NA	STR	NR	None	Yes
Quencer et al. 1979 [22]	22	M	Trigeminal nerve	NA	GTR	No	None	No
Miller et al. 1986 [21]	74	M	CPA	NA	GTR	NA	None	No
Beck et al. 1987 [11]	12	M	Meckel's cave into CPA	NA	NA	NA	Radiation	Yes
Carney et al. 1990 [13][a]	NA	NA	Trigeminal nerve	NA	NA	NA	NA	NA
Jensent et al. 1990 [19]	22	M	Orbit	NA	GTR	No	None	Yes
Earls et al. 1994 [18]	77	M	CPA	Isointense	STR	NA	NA	NA
Ranjan et al. 1995 [23]	56	F	CPA	NA	GTR	No	None	No
Buhl et al. 2004 [12]	28	M	CN V	NA	GTR	No	NA	NA
Zhang et al. 2005 [26]	11	M	CN III	NA	STR	NA	Radiation	No
Carrasco et al. 2006 [14]	34	F	CN V	NA	STR	NA	None	Yes
Mey et al. 2006 [20]	22	M	Orbit	Hypointense	GTR	No	Radiation	Yes
Er et al. 2007 [10]	54	M	Foramen magnum	Hypointense	GTR	No	None	No
Saint-Blancard et al. 2008 [24]	52	F	CPA	Hypointense	STR	Yes	None	NA
Scheithauer et al. 2009 [25]	41	F	Posterior fossa	NA	STR	Yes	Radiation	NA
Diaz Beveridge et al. 2010 [16]	60	M	Orbit	NA	GTR	NA	None	NA
Ditz et al. 2011 [17]	12	F	Orbit	NA	STR	No	None	Yes
Spina et al. 2015 [9]	47	F	CPA	Hypointense	STR	No	Radiation	NA
Present case, 2017	43	F	L. middle cerebellar peduncle	Hypointense	STR	Yes	Radiation	NA

STR subtotal resection, *GTR* gross total resection, *NA* not available, *M* male, *F* female, *CPA* cerebello-pontine angle, *CN* cranial nerves

[a]Two IMS cases reported in the same publication

found in the spine. It is not clear if both lesions originated simultaneously, or if one metastasized from the other [12]. Despite the paucity of data available, radical surgical excision should be attempted when possible. Of the 19 *IMSch* cases, 50% had recurrence rate in patients that had subtotal resection while gross total resection only had 25% recurrence rate [10]. Nevertheless, maximum surgical resection must be tempered with preservation of function. In our case, it was not possible to do a gross total resection without major neurological deficit, since the tumor was inherently attached to CN V, VII–XI, as well as the pons.

Necrosis is generally considered as one of the histopathological features of tumor aggressiveness. After a careful review of the literature, only three cases, including the present case, have reported necrosis [24, 25], (Table 1). It is interesting to note that in the cases where necrosis was reported, a subtotal resection was only achieved. At the same time, from the 19 cases, only 8 formally reported the absence of necrosis; from these, 6 cases had a gross total resection [9, 10, 12, 17, 19, 20, 22, 23] (Table 1). This is an interesting finding that raises the question, "Does the presence of necrosis induce melanotic schwannomas to be more adherent to nearby structures?". Further studies are needed to understand the effects of necrosis in MS and its adherent properties.

While there are no guidelines, review of the literature suggests that radiotherapy should be pursued especially when there is subtotal resection [10]. Given the recurrence rate and the metastatic potential, radiation has been strongly advocated by some authors especially if they display any features of malignancy [9, 11, 20, 25, 26]. There were 3 of the 19th reported *IMSch* cases where post-operative radiation showed disease control up to 48 months, and of those, only one case had a recurrence of tumor despite radiation [6, 13, 14]. Similarly, Zhang et al. reported 13 cases of extracranial *MSch* where they observed a lower rate of recurrence and metastasis in patients treated with Radiation postoperatively [6]. We have reviewed and discussed this research with the patient who decided to proceed with proton beam therapy. She is currently undergoing treatment.

Conclusion

Intracranial melanotic schwannomas should be part of the differential diagnosis for T2 hypointense tumors located at the skull base. Gross total resection should be pursued when anatomy allows. Although data is not yet significant, radiation therapy may be considered and further studied in patients with incomplete tumor resection.

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