Case Report

The "Pigmented Side" of Nerve Sheaths: Malignant Melanotic Nerve Sheath Tumor

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Abstract

Malignant melanotic nerve sheath tumor (MMNST) represents a highly aggressive neoplasm arising both in peripheral and cranial nerves. It accounts for < 1% of all nerve sheath tumors, but the real incidence may not be well defined yet because of the evolution of its nomenclature. To date, it is considered a distinct tumor type, no longer as the pigmented variant of schwannoma, with a different clinical course and biological behavior. MMNSTs exhibit a specific genetic hallmark related to the *PRKAR1A* gene, which explains the major incidence in Carney Complex-affected patients. One of the more frequent localizations is the paravertebral region, where it poses diagnostic concerns with both primary tumors arising from soft tissues and the meningeal covering, as well as metastatic ones (ie, melanoma). Herein we present a patient with an MMNST accompanied by the main clinical, radiological, histopathological, and molecular findings, stressing the need for a multidisciplinary diagnostic approach. To the best of our knowledge, this is the first report of proton beam therapy for MMNST. We also performed a literature review to collect and compare the more recent data in English literature and to highlight the "keep-in-mind" concepts to apply in a multidisciplinary diagnostic algorithm, with a focus on histopathology and related pitfalls.

Keywords

malignant melanotic nerve sheath tumor, melanotic nerve sheath tumor, pigmented lesions, malignant nerve sheath tumor

Introduction

Malignant melanotic nerve sheath tumor (MMNST) is a newly defined tumor type, thought to be derived from the neural crest cells,[1] affecting peripheral and cranial nerves that harbor an aggressive clinical course, accounting for < 1% of all nerve sheath tumors.[2] Before the WHO classification of Central Nervous System Tumors 5th edition, it was formerly known as melanotic schwannoma, further divided into 2 forms: nonpsammomatous tumors, affecting predominantly spinal nerves and paraspinal ganglia, and psammomatous melanotic schwannomas, these mainly arose from autonomic nerves, viscera, heart, and intestinal tract. MMNST is characterized by morphological features typically seen in other more frequent pigmented lesions, both arising as primary pigmented meningeal tumors (primary melanocytoma/melanoma) or metastatic ones. Given this morphological overlap with other neoplasms, especially in the case of metastatic melanoma, a correct diagnosis is required to direct patients toward the best treatment choice. One should consider that skin melanocytic tumors could be hidden until a metastatic onset, with frequent presentation in the central nervous system (CNS),[3] also including meningeal covering, as well as in various segments of peripheral nerve sheaths with a predilection for nerves' root. Another possible localization for metastatic melanoma is represented by soft tissues in paravertebral regions, so the differential diagnosis of a mass arising in spinal/paraspinal spaces should consider not only primary versus secondary neoplasms, but also tumors arising from/involving different tissues (nerve sheets, soft tissues, and meningeal covering). A particular finding to highlight is that MMNSTs are frequently associated with Carney complex (CC), an autosomal dominant genetic condition that leads to many different neoplasms, among which MMNSTs represent the main manifestation in the nervous system. The pathogenesis of CC is related to the presence of a heterozygous inactivated variant in

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the *PRKAR1A* gene that codes for the R1α regulatory subunit of protein kinase A (PKA), resulting in an overactivation of the cAMP/PKA pathway. As tumors related to CC, MMNSTs harbor almost always, also in sporadic presentations, inactivating mutations in *PRKAR1A*, with subsequent loss of PRKAR1A immunoexpression. This is an important tool to solve the problem of differential diagnosis in pigmented lesions of the central/peripheral nervous system.

Herein, we present a report of a 50-year-old woman with a 10-month history of progressive upper extremities radicular symptoms. After surgical excision, a diagnosis of spinal MMNST was made.

Furthermore, given the spectrum of possible differential diagnoses for a mass arising in the spinal and paraspinal regions, as above stated, we performed a literature review of MMNST/melanotic schwannoma published during the last 10 years, focusing on criteria to make a correct diagnosis, with the aim of shedding light on important pitfalls and clues in the complex diagnostic work-up of these lesions and adding relevant information on the best management strategy. Although a general attitude toward radiotherapy after surgical removal is rapidly emerging, the best timing and modalities remain to be defined, with no current guidelines for adjuvant therapies.

Materials and Methods

Histopathology

Tissue fragments were formalin-fixed and paraffin-embedded in a single block. Three hematoxylin–eosin slides were stained. The same block was used for immunohistochemistry purposes. 4-μm paraffin sections were dried at 80 °C for 15 min and stained on a Ventana BenchMark Ultra immunostainer (Ventana Medical Systems, Tucson, AZ, USA) using standard techniques. The following antibodies were applied: HMB45 (Ventana mouse monoclonal primary antibody, 790-4366), MART1 (Ventana A103 mouse monoclonal antibody, 790-2990), SOX10 (Cell Marque, Sp267 rabbit monoclonal primary antibody, 760-4968), S100 protein (Ventana polyclonal primary antibody, 760-2523), BRAF V600E (VE1) (Ventana mouse monoclonal primary antibody, 760-5095), BAP1 C-4 (Santa Cruz Biotechnology, mouse monoclonal IgG, sc-28383), and Ki67 (Ventana 30-9, rabbit monoclonal primary antibody, 790-4286). Slides were examined using a Leica DM 750 microscope equipped with a Leica ICC50 camera to capture digital images.

Molecular Pathology

To perform molecular and epigenetic characterization of the lesion, DNA was extracted with a Qiagen FFPE kit according to the manufacturer's instructions. DNA was sequenced with AmpliSeq for Illumina Cancer Hotspot Panel v2 (Illumina). The AmpliSeq for Illumina Cancer Hotspot Panel is a next-generation sequencing panel investigating somatic mutations across the hotspot regions of 50 genes with known associations to cancer, as identified in the Catalogue of Somatic Mutations in Cancer (COSMIC)1 database. Epigenomic characterization of tumor lesions was performed using Infinium Methylation EPIC BeadsChip Kit (Illumina technologies). To perform methylation analyses, 1000 ng of extracted DNA was converted using an EZ DNA Methylation Kit (Zymo Research). Raw IDAT files were analyzed by the bioinformatic freely available tool (DKFZ, https://www.dkfz.de/de/index.html).

Literature Review

A Medline search from 2013 up to 2023 in PubMed online electronic database was made. The following relevant keywords were used: "melanotic schwannoma," "malignant melanotic nerve sheath tumor," and "pigmented schwannoma." The inclusion criteria provided for case reports, case series, single institutional experiences, and reviews in the English language. We considered only papers describing tumors arising from spinal nerves and/or autonomic nerves in the paravertebral-midline region, then we excluded MMNSTs arising in visceral/perivisceral regions, that is, parotid gland,[4,5] submandibular gland,[6] gastrointestinal,[7] renal,[8] and para-renal localization,[9] cutaneous tumors,[10–14] head and neck tumors,[15–17] intracranial neoplasms.[2,18–23] Also, we excluded intraabdominal tumors without nerve root invasion[1] as well as pelvic,[24–26] retroperitoneal,[27] and peripheral nerve trunks[28,29] localizations.

We also excluded the study by Alamer because they reported patients between 2008 and 2015 at their institute[30] although the work was published in 2019 as well as Torres-Morra et al[31] which published their work in 2014 referring to a large cohort of melanotic schwannomas from 1992 to 2009; moreover, we excluded series focusing only on surgery[32] and/or radiology[33] or lacking detailed patients' data.[34] Finally, we excluded papers not available to download.[35,36] Additional studies were added based on a review of bibliographies of the identified papers. After duplicate removal, all abstracts were retrieved, and each article of interest was marked for further review. Demographic, clinical, pathologic, molecular, management, and outcome data were recorded.

Results

Case Presentation

A 50-year-old woman with no notable medical history presented to our institution with a 10-month history of

progressive upper extremities radicular symptoms: pain and tingling-like paresthesias initially in her left arm later extending contralaterally. On physical examination, she demonstrated the mild weakness of the left arm and leg, brisker osteo-tendinous reflexes in both arms, and sensitivity loss in the innervation territory of C6 in the left arm.

Magnetic resonance imaging (MRI) documented an extramedullary intradural neoplastic lesion at the level of C4 occupying the left aspect of the spinal canal and extending into the adjacent C4-C5 intervertebral foramen with associated bony remodeling. A marginal extraforaminal extension was also evident with mild compression on the longus capitis muscle. The lesion dislocated and compressed the spinal cord, which showed signs of compressive myelopathy at that level. It appeared inhomogeneously hyperintense on T1- and hypointense on T2-weighted sequences due to the presence of melanin pigment and methemoglobin blood products and showed marked enhancement after contrast administration. Findings were consistent with a spinal nerve sheath tumor (Figure 1 and Supplemental Figures).

Surgical treatment was recommended: tumoral resection was performed through a C4-C5 bilateral laminectomy, with the aid of intraoperative neuromonitoring. Under microscope visualization, the dura was opened on the midline and the proximal intradural aspect of the lesion was separated using standard microsurgical dissection from the cervical cord and removed "en bloc." The tumor appeared highly vascularized and of soft consistency. The most distal component of the tumor was identified and separated from the nerve proceeding in a distal-to-proximal direction toward its intraforaminal extension. Neuromonitoring revealed an appropriate electrophysiologic response during the entire surgical procedure, which was uneventful. During the postoperative course, neurologic symptoms improved with complete regression of the left arm and leg weakness.

Postoperative MRI, performed 7 days after the surgical procedure, showed surgical sequelae with excision of the lesion except for a small residual in the distal portion of the intervertebral foramen. At one-month radiological follow-up, a whole-body PET-CT scan demonstrated no evidence of metastatic pathological metabolism increment, whereas at MRI the residual cervical spine tumor significantly grew. The patient was referred to proton beam radiotherapy for further adjuvant treatment. At one-year clinical and radiological follow-up, neurological examination was normal with no evidence of residual tumor regrowth at MRIs.

Histopathology

Upon receipt of the specimen from the operating room, we described multiple soft-consistency fragments with a gray-white appearance. On microscopic examination (Figure 2) there were multiple fibrous fragments, plurifocally infiltrated by a hypercellular neoplasm composed of pigmented, medium-to-large-sized cells, with abundant eosinophilic cytoplasm, pleomorphic nuclei, prominent nucleoli and, focally, and nuclear pseudo-inclusions. There were no mitotic figures and/or necrosis.

An important finding was the presence of neurogenic tissue (Figure 2D) in the absence of normal nerve structures. On immunohistochemistry, tumor cells were HMB45+, MART1+, SOX10+, S100 protein +, and BRAF–; BAP1 was retained (Figure 3). The proliferative index Ki67 showed a labeling index of about 2% to 3%.

A diagnosis of MMNST was made. However, given the spectrum of differential diagnosis, we performed some sections for molecular analysis.

Molecular Pathology

Molecular analysis showed several somatic variants, as shown in Supplemental Table 5 (Supplemental File). No significant chromosomal aberrations are found by copy number analysis (Figure 4). The sample showed a strong match with the methylation tumor class of "melanocytic schwannoma."

Literature Review

The literature review has disclosed 40 patients with spinal MMNSTs/melanotic schwannoma.[15,20,37–66] The data of these reports are summarized in Tables 1 and 2, and Supplemental Tables 4 and 5 (Supplemental File Histology).

Epidemiological and Clinical Data. The patients were 23 men and 15 women (2 patients having no sex reported), with an age ranging from 18 to 72 years (median 42.6 years). Sensory/motor radiculopathies were the main symptoms, with the symptoms' distribution depending on the anatomic location (see below). Only 4 out of 19 patients performed genetic analysis: among these, a melanoma diagnosis was excluded searching BRAFV600E mutation in 2 tumors; 1 performed a complete genetic panel; 1 excluded CC and LiFraumeni. A total of 11 out of 19 patients were reported to not have other manifestations of CC nor to have many relatives with this diagnosis; for the others (8/19), this information was not reported.

Radiological Features. The MRI findings were specified in 37 patients, having carried out 1 patient only a PET/TC Total body and 2 only CT. Lesions were variably described. The imaging features are summarized in Table 1. When specified, all tumors were contrast-enhancing. In relation to the anatomic site, tumors were distributed as it follows: 8 cervical, 15 thoracic, 13 lumbar, and 4 sacral. According to the

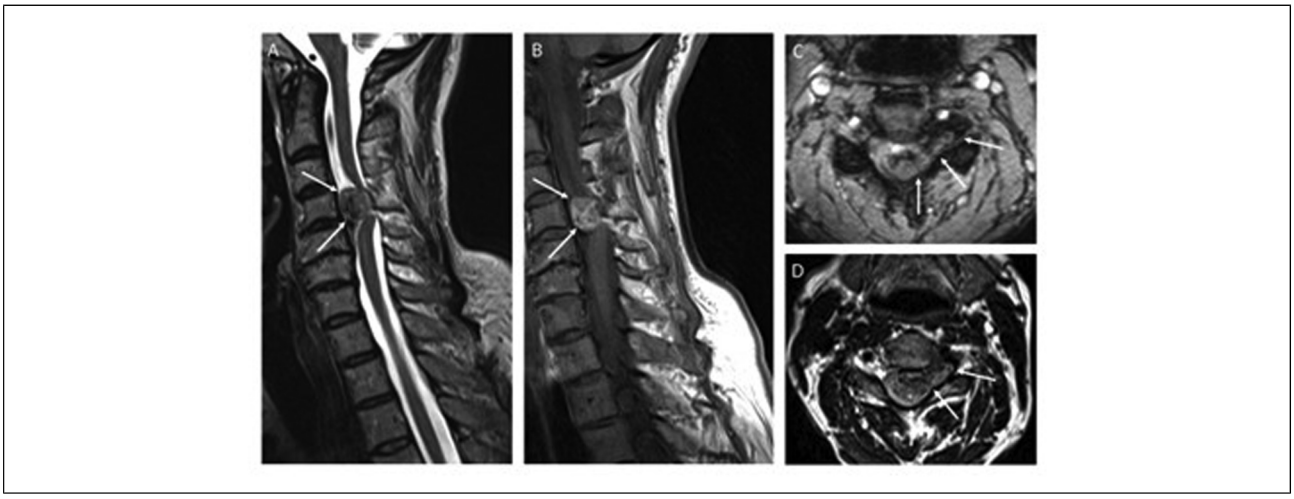

Figure 1. Magnetic resonance imaging. Sagittal T2- (A) and T1-weighted (B) images show an extramedullary intradural neoplastic lesion compressing the cervical spinal cord. The lesion is mainly hypointense on T2 and hyperintense on T1 due to melanin pigment. Axial T2*- (C) and T2-weighted sequences confirm these findings and demonstrate foraminal extension.

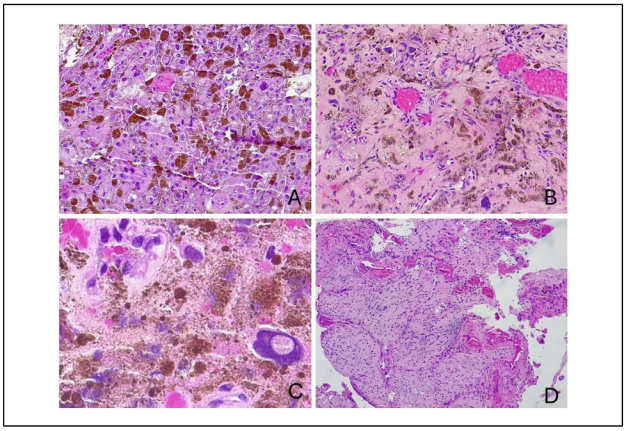

Figure 2. (A) Tumor cells were predominantly polygonal with well-defined borders, having abundant eosinophilic-to-clear cytoplasm, sometimes containing melanic pigment. In this field, nuclei were relatively uniform, with evident nucleoli (hematoxylin-eosin staining, original magnification 200 ×). (B) Tumor cells showed an infiltrative growth pattern (hematoxylin-eosin staining, original magnification 200 ×). (C) Some fields showed clear-cut features of anaplasia (hematoxylin-eosin staining, original magnification 630 ×). (D) It was evident the presence of neurogenic tissue (S100 +, not shown in this image) (hematoxylin-eosin staining, original magnification 100 ×).

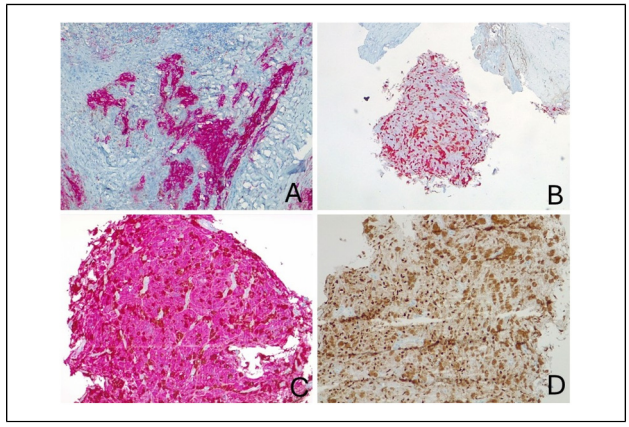

Figure 3. Using immunohistochemistry, tumor cells were HMB45 + (A, immunoperoxidase staining, original magnification 100 ×), MART1 + (B, immunoperoxidase staining, original magnification 40 ×), S100 protein + (C, immunoperoxidase staining, original magnification 100 ×), and SOX10 + (D, immunoperoxidase staining, original magnification 100 ×).

relationship with the spinal cord, the location was extramedullary in 34, intramedullary in 2, with an intraosseous component in 2 out of 3 sacral tumors (Table 2).

Management and Follow-Up. A total of 29 patients underwent surgical excision alone, 7 received surgery + RT, whereas 2 underwent surgery + RT + CHT. In one patient a diagnostic biopsy was performed, followed by systemic chemotherapy. One patient declined treatment. Follow-up was reported for 22/40 patients: 10/29 experienced recurrence, respectively, at 3 months,[63] 3 months,[38] 4 months,[46] 10 months,[55] 13 months,[43] 18 months,[60] 22 months,[42] 3 years,[55] 4 years,[44] and 6 years.[52] Two of the reported tumors were recurrence at the time of diagnosis,[48,53] but a follow-up was not documented. There was a high variability in follow-up timing. In one patient,[15] a cutaneous melanoma was diagnosed after melanotic schwannoma diagnosis.

Pathology. A total of 17/19 tumors were diagnosed as melanotic schwannoma, while the remaining 2 as MMNSTs.

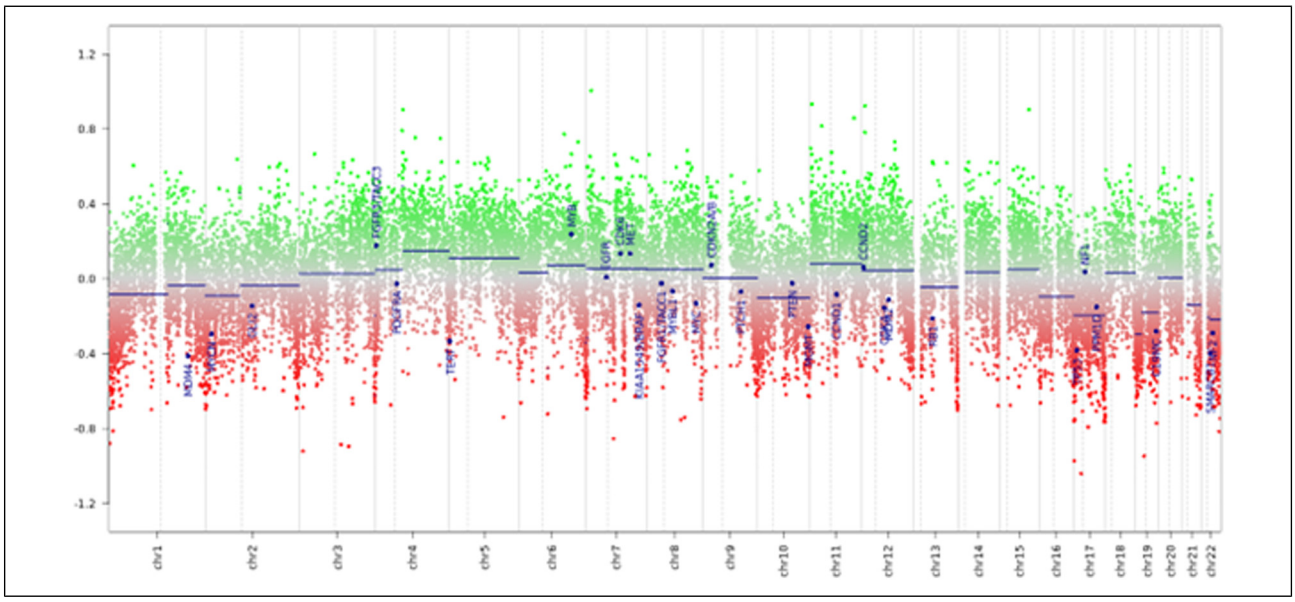

Figure 4. No significant chromosomal aberrations were found by copy number variation (CNV) analysis.

When the tumor pattern was described (17/40), it was reported as being composed of fascicles (6/17), sheets (2/17), and syncytia (1/17); the other tumors exhibited a mixed pattern (7/17), variably defined as composed of fascicle and sheets (4/7), lobules and fascicles (1/7), sheets and nests (1/7), and nest and cords (1/7). The more frequent patterns were mixed (7/17) and fascicular (6/17). The growth pattern was not specified in 23/40 tumors. Referring to cytology, tumors were composed of spindled cells (14/30), a mixture of spindled and epithelioid cells (15/30), and purely epithelioid ones (1/30). Tumor cytology was not clearly defined in 10/40 neoplasms. Only 5/40 tumors were defined as "pleomorphic." Mitotic count was documented only in 4 tumors, being low in all of them (1/10 HPF; 1/10 HPF; < 1/50 HPF; and 5/10 HPF mitoses). When a clear mitotic count was not reported, mitotic activity was defined as "low, hardly-to-found, absent, rare." Necrosis was reported only in 2/40 neoplasms.

Discussion

Several neoplastic,[67,68] degenerative, infectious, inflammatory, vascular, and traumatic diseases can affect the spine; among them, MMNST represents a newly defined tumor type, previously known as melanotic schwannoma. Since its first description,[69] around 200 tumors have been published in the literature,[43] with variable nomenclature: in 1932 Millar et al[70] described MMNSTs as melanocytic tumors of ganglion cells; in 1961, Hodson[69] suggested these neoplasms being a subtype of schwannoma, later named melanocytic schwannoma by Fu and co-authors.[49] So, until the new WHO CNS fifth edition, these tumors were considered a schwannoma subtype. Nearly two-thirds of reported tumors were part of Carney Complex43.

CC is an autosomal dominant syndrome characterized by pigmented skin lesions, skin and mucosal myxomas, and endocrinopathy. This syndrome is related in > 70% of patients to *PRKAR1A* inactivating gene mutations, coding for the R1a subunit of PKA, which leads to an overactivation of the cAMP/PKA pathway. MMNSTs represent the main CNS presentation in syndromic patients.[71]

MMNSTs arise predominantly in young adults (median age 33.2 years), and earlier in patients with CC (average: 22.5 years).[71] The most frequent localizations are represented by spinal and paraspinal nerves, including peripheral nerve trunks,[28] as well as the gastrointestinal tract. Posterior nerve roots are the most frequently involved site (30.5%)[15] while rare sites are represented by the cerebellum, orbit, heart, tracheobronchial tree, cervix, bone, soft tissue, and skin.[72] Intracranial tumors are quite rare: Spina et al[22] reported 18 tumors out of 105 melanotic schwannomas described in the literature. Among these, only 6 neoplasms involved the trigeminal nerve.

Symptoms are location-related: in fact, most patients usually present with a local mass with associated pain and neurologic symptoms depending on the anatomic site as well as on the rate of growth. Near to 35.5% of patients present with symptoms suggestive of spinal nerve involvement, which includes both motor and sensory abnormalities. Following progressive growth, the tumor may compress the spinal nerves and cause symptoms, such as tingling sensations, numbness, weakness, and pain in the lower limbs. Mass effect can cause mechanical dysfunction

of adjacent organs in 13% of patients. MMNSTs growing on the bone usually present as pain, along with a bony mass. Rarely, tumors may present acutely or subacutely over days to weeks.[37] Nearly 29% of patients are asymptomatic at presentation.[72,73]

Imaging plays an important role in the management of MMNSTs; it often represents the mode by which this tumor type is first detected, and diagnosis is first suggested. Also, imaging offers prognostic information from initial staging to posttreatment follow-up. The latter is relevant because histopathological features of MMNST are not predictive of outcome, as above stated. Thus, it is important for radiologists to be familiar with the imaging features of MMNST.[33] Until 1998, the MRI characteristics of MMNSTs had not been described: Bendszus et al[74] were the firstly to describe MMNSTs characteristics on MRI. Since then, MR imaging has remained the gold standard among diagnostic procedures for these tumors. These lesions typically appear spontaneously hyperintense in T1-weighted images and hypointense in T2-weighted images[15,46,72] due to paramagnetic free radicals in melanin. This is an important finding that helps in distinguishing MMNSTs from schwannomas using MRI.[72]

On pathologic examination, MMNSTs are circumscribed but unencapsulated tumors, composed of plump spindled and epithelioid cells, arranged in interlacing fascicles or nests with marked accumulation of melanin in neoplastic cells and associated melanophages.[72] The pigment is positive for the Fontana-Masson melanin silver stain but negative for Prussian blue and periodic acid-Schiff (PAS) stains. Cytologically nuclei are round, ovoid, or elongated and contain delicate evenly distributed chromatin with distinct nucleoli. In some cells, the nucleoli are large and prominent. Mitotic count is usually low, unlike malignant melanoma. MMNSTs can present with psammoma bodies that may be focal and only identifiable after an extensive search. These tumors usually lack Verocay bodies, microcysts, and thick-walled hyalinized blood vessels, differently from Schwannomas. Melanotic schwannoma with degenerative nuclear atypia, containing scattered cells with markedly enlarged, hyperchromatic nuclei, often with ''smudgy'' chromatin, and cytoplasmic nuclear inclusions may also be present on occasion. Necrosis, if present, is often geographic. Strict criteria of malignancy in MMNSTs are not well defined, although a worrisome combination of histologic features (large, vesicular nuclei with macronuclei; brisk, mitotic activity; and necrosis) raises concern about aggressive behavior. Anyway, MMNSTs may have a malignant clinical course even in the absence of the classic histologic criteria of malignancy. Recurrence and metastases are observed even 20 years after diagnosis, with the lung being the main metastatic site.[13] Immunohistochemically, tumors are positive for S100 protein, SOX10, HMB-45, Melan-A, p16, and vimentin and there is usually loss of PRKR1A immunohistochemical expression. Ultrastructurally, it can be demonstrated the presence of numerous elongated tumor cell processes, duplicated basement membranes, and melanosomes.[72]

The main differential diagnosis is with primary CNS melanocytomas and melanomas, as well as with metastatic pigmented lesions, primarily cutaneous melanomas. Primary CNS-pigmented lesions can harbor a broad spectrum of histopathological features, ranging from tumors with cytologically bland cells to frankly malignant melanomas. Melanomas, both primary and metastatic, are usually more pleomorphic and mitotically active and may have a higher cellular density, unlike lower-grade lesions. Psammoma bodies, if present, are essentially diagnostic for MMNSTs.

The utility of IHC in the distinction between MMNSTs and melanocytomas/melanomas is limited, since both MMNSTs and melanomas express melanocytic markers like HMB-45 and Melan-A.[72,75] However, as above stated, MMNSTs are related to PRKAR1A mutations, with a typical loss of PPKAR1A immunoexpression.[76] Given what has been said so far, we suggest a diagnostic work-up based on the integration of clinical, radiological, and morphological pitfalls and clues, supported by the advancements in molecular analysis (Table 3): MMNSTs arise from spinal or autonomic nerve, which are often detectable via MRI, whereas meningeal melanocytomas/melanomas arise from meningeal covering. A metastasis from cutaneous melanoma should be considered in a patient with a history of malignant/atypical skin-pigmented lesions. Nevertheless, a complete skin examination may be clinically performed to rule out a nondiagnosed skin melanoma. If doubt remains, however, genetic studies may be helpful: MMNSTs do not harbor the frequent BRAF mutations of melanoma or GNAS mutations of melanocytoma.[46] It has been suggested that combined morphological and GNAQ mutational analyses should be used to discriminate MMNST from other primary melanocytic lesions.[77]

The aim of surgery should consider an onco-functional balance, between the need for gross total tumor resection to decrease the risk of recurrence, and the need to preserve/restore or arrest the worsening of clinical symptoms through decompression of nervous structures.[78,79]

Surgical resection aiming at tumor total removal is the treatment of choice of spinal MMNSTs. However, these tumors often involve the nerve roots and are infiltrative, with the need to preserve the function limiting the extent of resection is the treatment of choice. Regarding the use of adjuvant radiotherapy, our results show that its role remains controversial, with only 5/17 patients (29.4%) receiving it and most studies suggesting radiotherapy only following local recurrence or distal metastases. Nevertheless, the local recurrence rate of 15% and metastasis rate of 23% in our study, despite the short follow-up

Table 1. Main Clinic-Radiological Data Reported by Selected Studies.

Patient	Author	Date	Patient age and sex	Symptoms	Localization	Imaging	Treatment	Genetic analysis	Family history	Diagnosis	Follow-up
1	Mahesh et al	2014	67, M	Paraparesis for 2 weeks	Intradural intramedullary D2-D10	**MRI:** T1 hyper T2 iso; contrast enhancing	Surgery + RT	NR	NR	Melanotic schwannoma	1-year follow-up uneventful
2	Faria et al	2013	32, W	6-month history of cervical pain and left arm progressive weakness	Intradural-extramedullary C4-C5	**MRI**: T1 hyper; T2 iso	Surgery + RT + CHT	NR	No	Melanotic schwannoma	3 mo after surgery, local recurrence + lung metastases. Death after 3 mo from diagnosis
3	Mohamed et al	2014	43, M	Left leg weakness	Intradural thoracic T9-T10	**MRI:** contrast enhancing	Surgery	NR	NR	Melanotic schwannoma	3 mo uneventful
4	Li B et al	2015	62, M		7th thoracic spinal body intraspinal to paravertebral	**CT:** Well circumscribed dumb-bell shape tumor	Surgery	NR	NR	Melanotic schwannoma	No recurrence nor metastasis after 30 months follow-up
5	Shanmugam et al	2015	67, M	Weakness and numbness in both lower limbs for 2 months	Intradural, extramedullary D8-D12	**MRI:** intradural, extramedullary lesion	Surgery	CC	NR	Melanotic schwannoma	NR
6	Bakan et al	2015	31, W	Back pain	T4-T5 foramen/ spinal canal	**MRI**: focal T1 hyper; contrast enhancing. *Cystic component:* T1 hypo, T2 **CT**: punctate calcifications. **PET/CT:** no metastasis	Surgery	NR	NR	Melanotic schwannoma, psammomatous	6 months follow-up uneventful
7	Chen et al	2015	47, M	Chest and back pain	T2-T4 subdural extramedullary	**MRI:** T1 hypo, T2 hypo; contrast enhancing	Surgery	NR	NR	Melanotic schwannoma	Uneventful 6 months
8	Shabani et al	2015	54, M	Incidental finding	Left C-5 foramen	**CT**: well-defined, ovoid lesion. **MRI** contrast enhancing	Surgery	BRAF not contributed	NR	Melanotic schwannoma	Recurrence after 18 months
9	Guzel et al	2016	36, M	Low back pain	Estraspinal L5-S1 foramen	**MRI:** T1 and T2 hper	Surgery	NR	NR	Melanotic schwannoma	Uneventful 6 months
10	Khoo et al	2016	36, W	4-year history of left hip pain	Left L5 nerve root	**MRI**: hyper T1, mixed heterogeneous T2	Surgery	NR	NR	Melanotic schwannoma	After 10 months regrowth and skip metastasis in ilium
11	–	2016	20, NR	4-year history of lower back	S1, Osseous component	**MRI:** T1 hyper T2 hypo; mild contrast enhancement	Surgery	NR	NR	Melanotic schwannoma	No follow-up

(continued)

Table 1. (continued)

Patient	Author	Date	Patient age and sex	Symptoms	Localization	Imaging	Treatment	Genetic analysis	Family history	Diagnosis	Follow-up
12	–	2016	46, NR	2-year history of back and left leg pain	L3 foraminal	**MRI**: T1 and T2 hyper	Surgery + CHT + RT (after metastasis)	NR	NR	Melanotic schwannoma	Multiple recurrence and metastasis for 3 years follow-up
13	Choi et al	2017	59, M	Right buttock pain	L4 level	**MRI:** destructive mass of the vertebral body	Surgery	NR	NR	Melanotic schwannoma	This was a recurrence. At the time patient had pulmonary metastasis
14	Tatsi et al	2017	36, M	Low back pain	L5-S1 neural foramina	**MRI:** T1 and T2 hyper	Surgery	Tumor sample on exon 5 of the GNA11; no germline mutation	NR	Melanotic schwannoma	No recurrence after 6 months
15	Keskin et al	2017	42 yo, M	Hypertension	Extraspinal paravertebral Near to right adrenal gland	**TC:** well-defined with calcifications	Surgery	NR	NR	Melanotic schwannoma	NR
16	–	2017	22yo, W	Incidental	Intradural extramedullary L1-L2	**MRI:** T1 hypo, T2 hyper	Surgery	NF2	NR	Melanotic schwannoma	NR
17	Cheng et al	2018	47, M	Back pain	Intramedullary T4-T5	**MRI:** T2 hyper	Surgery	NR	NR	Melanotic schwannoma	Recurrence after 6 y
18	Chandran et al	2018	35, M	Back pain and foot drop	L2-L3 intradural extramedullary	**MRI** Contrast enhancing T1	Surgery	No	NR	Melanotic schwannoma	This was a recurrence
19	–		25, M	Neck pain	C2 vertebral level	**MRI**: T1 hypo; contrast enhancing.	Surgery	No	NR	Melanotic schwannoma	No recurrence after 5-years follow-up
20	Zaninovich et al	2019	22, M	AFP and complete loss of sacral function	Extradural extramedullary lesion, T9-T11	**MRI**: T1 iso with faint patches of T1 hyper	Surgery	No	NR	Malignant melanotic schwannoma	NR
21	Li et al	2019	61, W	3-year history of progressive weakness of the lower limbs	Intramedullary, spinal canal at the level of L1	**MRI**: cystic-solid mass. *Cystic component*: T1 hypo, T2 hyper. Eterogeneously CE. *Solid component*: T1 iso, T2 iso. Eterogeneously CE	Surgery	No	No	Melanotic schwannoma	
22	Velz et al	2019	32, W	2-y history of intermittent thoracic and abdominal pain	Intraspinal canal, T10-12 nerve roots.	**MRI**: Encapsulated, multilobulated mass	Surgery + RT	BRAF V600E neg	No	Melanotic schwannoma	*3 mo follow-up FDG-PET total body*: 3 lesions in the abdominal fat, highly suspicious of metastasis

(continued)

Table 1. (continued)

Patient	Author	Date	Patient age and sex	Symptoms	Localization	Imaging	Treatment	Genetic analysis	Family history	Diagnosis	Follow-up
23	Nagashima et al	2020	48, M	6-month history of low back pain and left sciatic pain.	Left S2 nerve root, with bone extension	**MRI**: T1 hyper, T2 Hypo. CE	Surgery	No	No	Melanotic schwannoma	*NR*
24	Solomou et al	2020	45, W	One-year history of neck pain	C6 nerve root, with both intradural and extradural components	**MRI:** T2 hypo; contrast enhancing	Surgery + RT	BRAF V600E negative	No	Melanotic schwannoma	Patient was diagnosed with a cutaneous melanoma pT1a after an MS diagnosis
25	Biju et al	2020	38, W	Lower back pain	left L5/S1 neural exit foramen.	**MRI:** well-circumscribed lesion within the foramen with some extraforaminal extension	Surgery	No	No	Melanotic schwannoma	NR
26	Hou et al	2020	53, W	2-year history of neck pain and upper extremity numbness and weakness	C1 and C2 vertebral bodies in the right spinal canal	**MRI**: T1 and T2 hypo	Surgery + RT	No	NR	Melanotic schwannoma	NR
27	Takatori et al	2020	39, M	Low back pain and numbness of the left leg	Intradural extramedullary L4 level	**MRI**: T1 hyper T2 hypo	Surgery	No	NR	Melanotic schwannoma	The patient died 22 months after surgery. Multiple lung metastasis, spinal cord, bilateral chest wall, and stomach
28	Georgiev et al	2021	61, M	History of low back pain	L3 rootlet, intradural extramedullary	**MRI**: T1 hyper T2 hypo	Surgery	No	No	Melanotic schwannoma	Recurrence 13 months after surgery
29	Shen et al	2021	29, W	Backache	L2-L3 spinal root	**PET/TC:** strong FDG uptake	Puncture biopsy + CHT	No	No	Melanotic schwannoma	4 years later tumor recurrence + pulmonary metastasis
30	Morgan et al	2021	50, W	asymptomatic right neck lump	C8 nerve root, extradural extraforaminal	**MRI**: nonenhancing	Surgery	No	No	Melanotic schwannoma	NR
31	Shui C. et al	2022	21, W	3 months of left L5 distribution radicular leg pain and sensory loss	Left L5/S1	**MRI:** dumbbell-shaped, heterogeneously enhancing	Surgery	No	NR	MMNST	4 months later MRI showed diffuse leptomeningeal enhancement
32	Yeom JA et al	2022	58, M	Low back pain, paresthesia, and cold sensation	Intradural extramedullary mass lesion T11-T12	**MRI**: T1 hypo, T2 hyper	Surgery	No	No	Melanotic schwannoma	NR

(continued)

Table 1. (continued)

Patient	Author	Date	Patient age and sex	Symptoms	Localization	Imaging	Treatment	Genetic analysis	Family history	Diagnosis	Follow-up
33	–	2022	72, M	6-mo history of low back pain and paresthesia in both legs	Intramedullary mass lesion T11	**MRI**: T1 hyper, T2 hypo	Surgery	No	No	Melanotic schwannoma	NR
34	Yan et al	2022	35, M	Low back pain and	S2 spinal canal with intraosseous component	**MRI**: T1 hypo/hyper T2 inverse signal; contrast enhancing	Surgery + RT	No	NR	Melanotic schwannoma	NR
35	Hall et al	2022	18, W	Progressive lower back	S1 nerve root	**MRI**: T1 hyperintense/ T2 hypointense	Surgery + RT	Yes. CC e Li-Fraumeni was excluded	No	Melanotic schwannoma	NR
36	Bonomo et al	2023	28, M	Cervical pain radiating to the right arm.	C5-C6 and C6-C7 extradural	**MRI**: T1 hyper, T2 hypo, contrast-enhancing	Surgery	Yes, an extensive genetic panel	No	MMNST	1-year follow-up uneventful
37	Grandmougin et al	2023	31, W	Dysesthesia around the neck.	C2-C3 intradural extramedullary	**MRI**: T1 hyper; T2 hypo	Surgery	Yes, diagnosis of CC	No	Melanotic schwannoma	NR
38	Sun et al	2023	55, W	Right waist to hip swelling pain	Intradural intramedullary D2-D10	**MRI:** T1 hyper, T2 hypo	Surgery + RT	NR	NR	Melanotic schwannoma	1-year event free
39	Xiang et al	2023	60, M	2-year history of chest and back pain	Intraspinal-foramen T6-T7	**MRI:** T2 hyper T2 iso; inhomogeneous CE	Patient declined treatment	Mo CC	NR	Melanotic schwannoma	NR
40	McCann et al	2023	40, M	2-month history of progressive bilateral leg weakness and pain that	Intramedullary T8-T11	**MRI**: contrast enhancing	Surgery	NR	NR	MMNST	3 months uneventful

Abbreviations: CE, contrast enhancement; W, woman; Hyper, hyperintense; Hypo, hypointense; iso, isointense; M, man; MMNST, malignant melanotic nerve sheath tumor; mo, month/months; NR, not reported; RT, radiotherapy; y, year/years; yo, years old.

Table 2. Results of Review.

Number of patients	40
Sex	
M	23
F	15
NR	2
Mean age	42.6
Localization	
Extramedullary	34
Intramedullary	6
Anatomic site	
Cervical	8
Thoracic	15
Lumbar	13
Sacral	4
Genetic analysis	
Y	10
N/NR	30
Treatment	
Surgery alone	29
Surgery + RT	7
Surgery + RT + CHT	2
Biopsy + CHT	1
Declined treatment	1
CC association	1
Follow-up	
Not reported	18
Reported	22
Recurrence	
Y	10
N	12
Histology	
Melanotic schwannoma	37
MMNST	3

Abbreviations: NR, not reported; RT, radiotherapy; CHT, chemotherapy; MMNST, malignant melanotic nerve sheaths tumor; Y, yes; N, no.; CC, Carney complex.

Table 3. Main clinical, Morphological, and Genetic Keypoints to Kept in Mind for a Differential Diagnosis Among MMNSTs, Meningeal Melanomas/Melanocitomas, and Metastatic Melanomas.

Malignant melanotic nerve sheath tumor	Meningeal melanocytoma/ meningeal melanoma	Metastatic melanoma
• Spinal or autonomic nerves • Both Schwann cell and melanocytic differentiation • **PRKR1A mutations** • **No GNAQ or GNA11** • **No BRAF, NRAS, TERT**	• Arises from meningeal covering • **No PRKR1A mutations** • **GNAQ or GNA11** • **No BRAF, NRAS, TERT**	• History • **No PRKR1A mutations** • **No GNAQ or GNA11** • **BRAF, NRAS, TERT**

Red color identifies the main molecular alteration in that specific tumour type. Bold text highlights molecular features in table.

(average 18 months only), confirm the malignant clinical behavior of spinal MMNSTs. Other authors emphasize the role of adjuvant radiotherapy, especially in the case of subtotal resection, reducing the rate of relapse and metastasis. OuYang et al[27] observed a lower rate of recurrence and metastases in patients with MMNSTs treated with adjuvant radiotherapy. According to these authors, radiotherapy should be considered in the presence of histologic criteria of malignancy, incomplete surgical resection, tumor recurrence, or metastases. The patient reported by Hou et al[41] showed a recurrence after a surgical-radiotherapeutic treatment, without gross total resection. Thus, even when adjuvant radiotherapy is performed, close observation should be continued. For our patient, a strict radiological follow-up was scheduled after subtotal resection, and radiotherapy was performed in the evidence of tumor regrowth. Based on our experience and given the metastatic potential of MMNST, we suggest that whenever residual disease is left, adjuvant radiotherapy is appropriate.[76] Uncertainty with adjuvant radiotherapy is more likely related to the lack of robust data demonstrating its efficacy due to the rarity of the disease. Fractionated radiotherapy is a suitable option for MMNST close to susceptible structures, such as the spinal cord. Our patient was referred to proton beam therapy because of the unique ballistic characteristics of high-energy particles that allow dose escalation to the tumor and delivery of substantially lower doses to critical structures compared to other radiation modalities.[80]

Despite encouraging data no clinical series have been published to date regarding the effectiveness of radiotherapy, and no treatment protocol is available. This is the reason why our multidisciplinary team proposed, given the GTR, a follow-up without radiotherapy.

Conclusion

Spinal MMNSTs pose the challenge of a complex diagnostic work-up, both because of the wide differential diagnosis, requiring nerve sheath and other melanocytic tumors exclusion, and the therapeutic and prognostic repercussions. We recommend the integration of clinical history, accurate imaging description, morphological findings, immunohistochemistry, and molecular analyses to make a correct diagnosis. Although the effectiveness of adjuvant therapy is still debated, the potential malignant behavior of these tumors suggests the need for further treatment, especially in the case of subtotal resection. Proton beam therapy is an attractive option, reducing the toxicity to nearby critical neural structures. Further studies and longer follow-

ups are required to better define its role in the management of MMNSTs.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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