When "Peripheral" Becomes "Central": Primary and Secondary Malignant Intracerebral Nerve Sheath Tumor: A Case Report and a Systematic Review

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BACKGROUND: The intracerebral occurrence of malignant peripheral nerve sheath tumors (MPNSTs) is exceedingly rare, and despite aggressive treatments, local recurrence and poor prognosis are very frequent. Like other brain tumors, these tumors could be primary or secondary, making the term "peripheral" an imprecise term for a primary brain tumor.

OBJECTIVE: To analyze the reported cases of primary and secondary cerebral MPSNTs in terms of diagnosis, treatment, and overall survival. Additionally, we present a case of malignant intracerebral nerve sheath tumor (MINST) treated with radical surgery and radiotherapy.

METHODS: Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, one database (PubMed) and crossed references were queried for MPNST with brain metastasis and primary MINSTs from 1971 to 2020. Data regarding demographic features, primary tumor site, risk factors, brain location of the lesion, treatment applied, and overall survival were extracted.

RESULTS: A total of 55 patients were selected (including the reported case): 29 patients were secondary brain MPNST and 26 patients were primary MINST. The mean age was 41.8 ± 22 and 31.2 ± 23 yr, respectively. All brain metastases of MPNST (100%) had a primary tumor elsewhere in the body at the time of diagnosis. The overall survival was significantly shorter in patients with a secondary brain MPNST compared to MINST ($P = .002$).

CONCLUSION: We present a comprehensive analysis of every reported primary and secondary intracerebral MPNST. The prognosis in terms of survival is worst in the last one despite aggressive treatment. The lack of a primary MPNST in screening tests is sufficient to confirm a MINST at time of diagnosis.

KEY WORDS: Brain sarcomas, Brain metastasis, Malignant schwannomas, Metastatic MPNST, MINST, Nervi vasorum, Radiosurgery

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Malignant peripheral nerve sheath tumors (MPNSTs) are rare mesenchymal tumors, representing 5% to 10% of all soft tissue sarcomas.[1] The World Health Organization (WHO) coined the term MPNST, replacing previous heterogeneous and often confusing terminology, such as malignant schwannoma, malignant neurilemmoma, and neurofibrosarcoma, for tumors of neurogenic origin and similar biological behavior.[2-4]

These highly aggressive tumors can originate from peripheral cells or the sheath of peripheral and cranial nerves.[5] More than half of MPNST cases develop in patients with NF-1, and there is a higher incidence in patients who have undergone prior radiotherapy.[6-8] The overall survival and prognosis of these tumors is poor, and despite aggressive treatments, local recurrence and distant metastases are common, worsening even more the prognosis and survival.[9-12]

ABBREVIATIONS: CNS, central nervous system; **GTR,** gross total resection; **MINST,** malignant intracerebral nerve sheath tumor; **NPS,** nonparaspinal; **PRISMA,** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PS,** paraspinal; **SSII,** survival since intracerebral involvement; **STR,** subtotal resection

Even though these tumors are more frequent in the trunk and limbs, their intracranial counterparts are even more sporadic and are more likely to develop from normal neural tissue, including precursor schwannomas.[13] They could be divided into extra-axial and intraparenchymal.[14] The intraparenchymal tumor is formally named malignant intracerebral nerve sheath tumor (MINST) and is exceedingly rare,[15] but the occurrence of a brain metastasis of a MPNST in another site is also a differential diagnosis.[12]

In this review, we analyze the current literature of primary and secondary intracerebral MPNSTs. We described demographic characteristics, risk factors, treatment modalities, histologic features, and survival of every reported case. Additionally, we present a case of a MINST in a young female treated in our institution.

METHODS

Search Method

The current systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] A systematic search was conducted in the PubMed/Medline databases using the following terms: "malignant peripheral nerve sheath tumor," "brain metastasis," "malignant schwannoma," "neurofibrosarcoma," "metastatic MPNST," "intracranial metastasis," "malignant intracerebral nerve sheath tumor," and "intraparenchymal MPNST." Any discrepancies were resolved through consensus. Search strategy is reported in Figure 1.

Selection Criteria

Including criteria were as follows: (1) the study must be a case report, case series, prospective cohort, retrospective case-control study, or systematic review published in English, Spanish, French, or Portuguese between 1971 (first reported brain metastasis of MPNST) and March 2020 when the query was performed; (II) the studies must have reported presence of MPNST with intracerebral metastasis or a MINST; (III) the study must have reported age, sex, site of primary tumor, time to brain metastasis, pathological findings, risk factor, and treatment modality applied to the patient; and (IV) studies must not have overlapped patients and have full text available at University of Miami.

Patients reported with a primary extra-axial MPNST were excluded. In the same way, brain invasion by contiguity of a primary extra-axial tumor were excluded because by definition they are not considered a distant metastasis.[17]

Case Presentation

In addition to our systematic review, we report a patient with a MINST managed at our institution. To participate, prior informed consent from the patient was obtained. The patient consented for publication of the present manuscript. The study was performed in accordance with the institution's Human Research Protection Office guidelines.

Data Abstraction

The extracted variables of each patient included the following: age, sex, primary MPNST site, time interval to brain metastasis, risk factors for MPNST, immunohistochemistry, cerebral location of the tumor, treatment modality applied, and survival since intracerebral involvement (SSII).

Primary MPNST site refers to any anatomic site outside the brain and spine. Malignant cranial nerve schwannomas were not included. For statistical purposes, primary tumor site in secondary MPNSTs was considered a dichotomic variable according to their proximity to the dural sac (paraspinal MPNST [PS-MPNST] vs nonparaspinal MPNST [NPS-MPNST]).

The surgical results were classified into gross total resection (GTR), subtotal resection (STR), or biopsy. Time interval to brain metastasis is the time in months from the former diagnosis of an MPNST to the brain involvement. A metastatic tumor could be described in another site before the central nervous system (CNS) involvement, but this time was not considered. SSII refers to the survival time from the diagnosis of the CNS tumor to the death of the patient due to any cause.

Statistical Analysis

The primary endpoint was CNS involvement with a primary or secondary MPNST. Variables were analyzed using GraphPad Prism 6 (GraphPad Software, San Diego, California), and graphics were made using Microsoft Excel 365 (Microsoft, Redmond, Washington).

Categorical variables were presented as proportions and the continuous variables were presented with mean and standard deviation. Nonparametric Mann-Whitney test was used to assess the relationship between primary tumor site and the time to develop a brain metastasis. The site of the brain tumor was considered a dichotomic variable (supratentorial vs infratentorial).

Regarding the survival analysis (SSII), a univariate analysis for overall survival was performed using the Kaplan-Meier method. The stratified log-rank test was used to compare treatment results in each variable group. A *P*-value of .05 or less was statistically significant.

RESULTS

Case Report

A 38-yr-old woman presented with progressive symptoms of facial and arm weakness. Her past medical history was remarkable for triple negative breast cancer (BRCA-1 mutation positive) treated with surgery, chemotherapy, and radiotherapy in 2019. Since then, her breast cancer was in remission. A brain magnetic resonance imaging (MRI) (Figure 2A and 2B) demonstrated a right frontal lobe mass with heterogeneous enhancement. Considering her past medical history, breast cancer brain metastasis was highest in the differential diagnosis.

Elective surgical resection was performed, and a GTR was achieved while preserving motor function (Figure 2C and 2D). Histopathologic examination showed typical features of nerve sheath tumor (Figure 3): arrangement of spindle cells in interlacing fascicles with marked cellular polymorphism, high mitotic rate, and focal necrosis. According to the French Federation,[18] these pathological findings corresponded to a grade 3. Immunohistochemistry showed that the tumor cells were positive for S-100, SOX10, and EMA. Postoperatively, she received stereotactic radiosurgery with a total dose of 18 Gy (Gamma Knife, Elekta, Stockholm, Sweden) to the resection cavity. No chemotherapy was administered. On physical examination, there were no signs

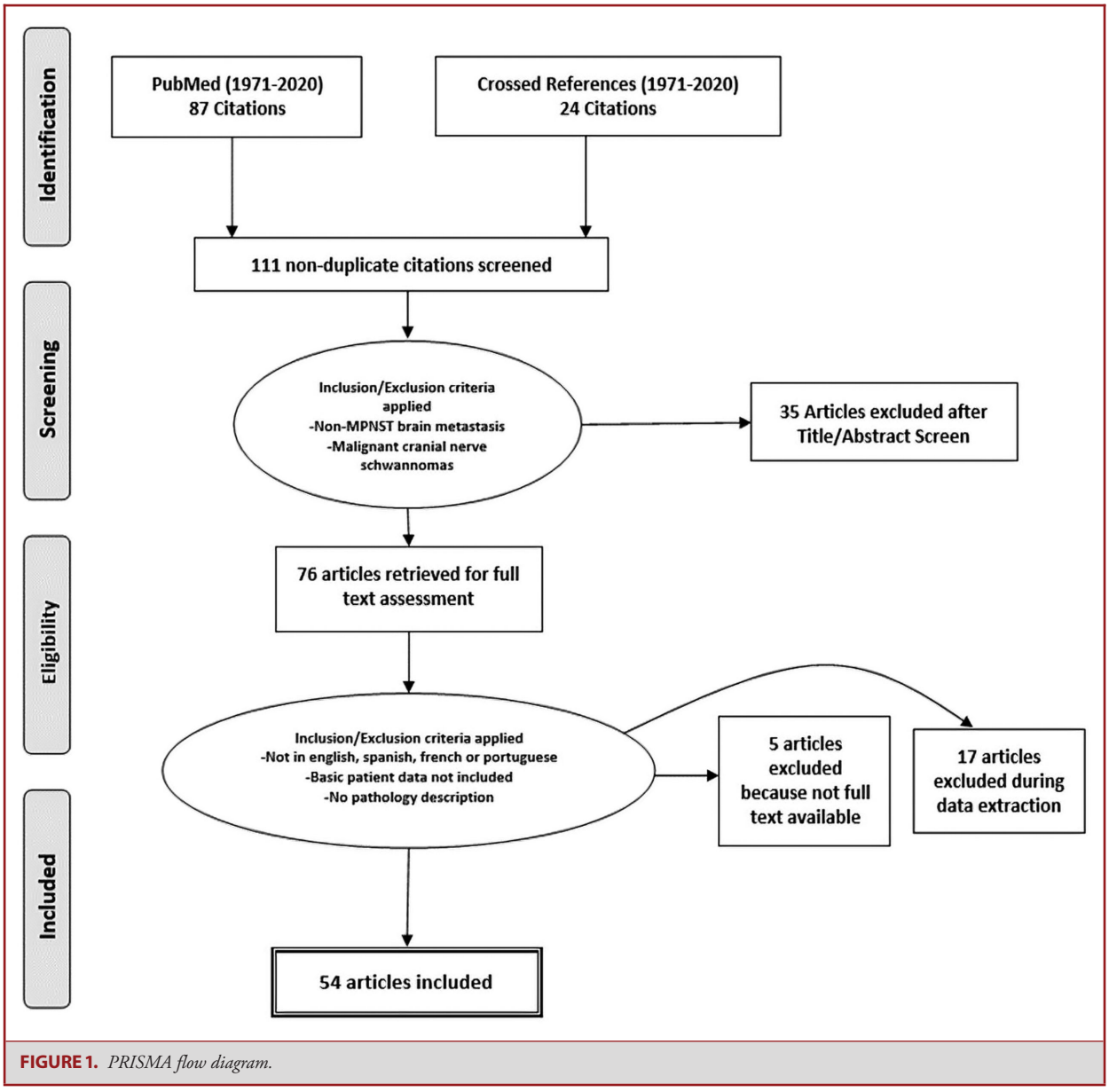

FIGURE 1. *PRISMA flow diagram.*

of phacomatosis and a thorough family history for NF-1 screening was negative.

Because of her history of 2 malignant tumors and the BRCA-1 mutation, a genetic assessment was performed to rule out NF-1 mutation or other germline mutation. NF-1 phenotypes are extremely variable, and NF-1 gene and BRCA-1 genes are both on chromosome 17, about 20 centiMorgan (cM) apart.[19] In order to impact both genes, there would have to be a gross chromosomal deletion involving many genes in between the two and would likely cause more phenotypic abnormalities. A multigene next generation sequencing panel (Invitae Corporation, San Francisco, California) confirmed no mutation on NF-1 gene, but after gene sequencing (Foundation One Heme, Roche Diagnostics, Cambridge, Massachusetts), we found a deletion in exons 37-39, a novel mutation in patients with neurofibromatosis.[20,21]

Because of the rarity of a primary intracranial MPNST, a whole-body 18Ffluorodeoxyglucose positron emission tomography (FDG-PET) (Figure 4) and CT scan were performed 1 mo after surgery. The results were negative for the presence of pathological mass or FDG uptake in any part of the body, focusing on the chest.

Six months after surgery, another CT scan and FDG-PET were negative for any pathological mass. However, a follow-up brain MRI showed a right frontobasal dural metastasis. The oncology

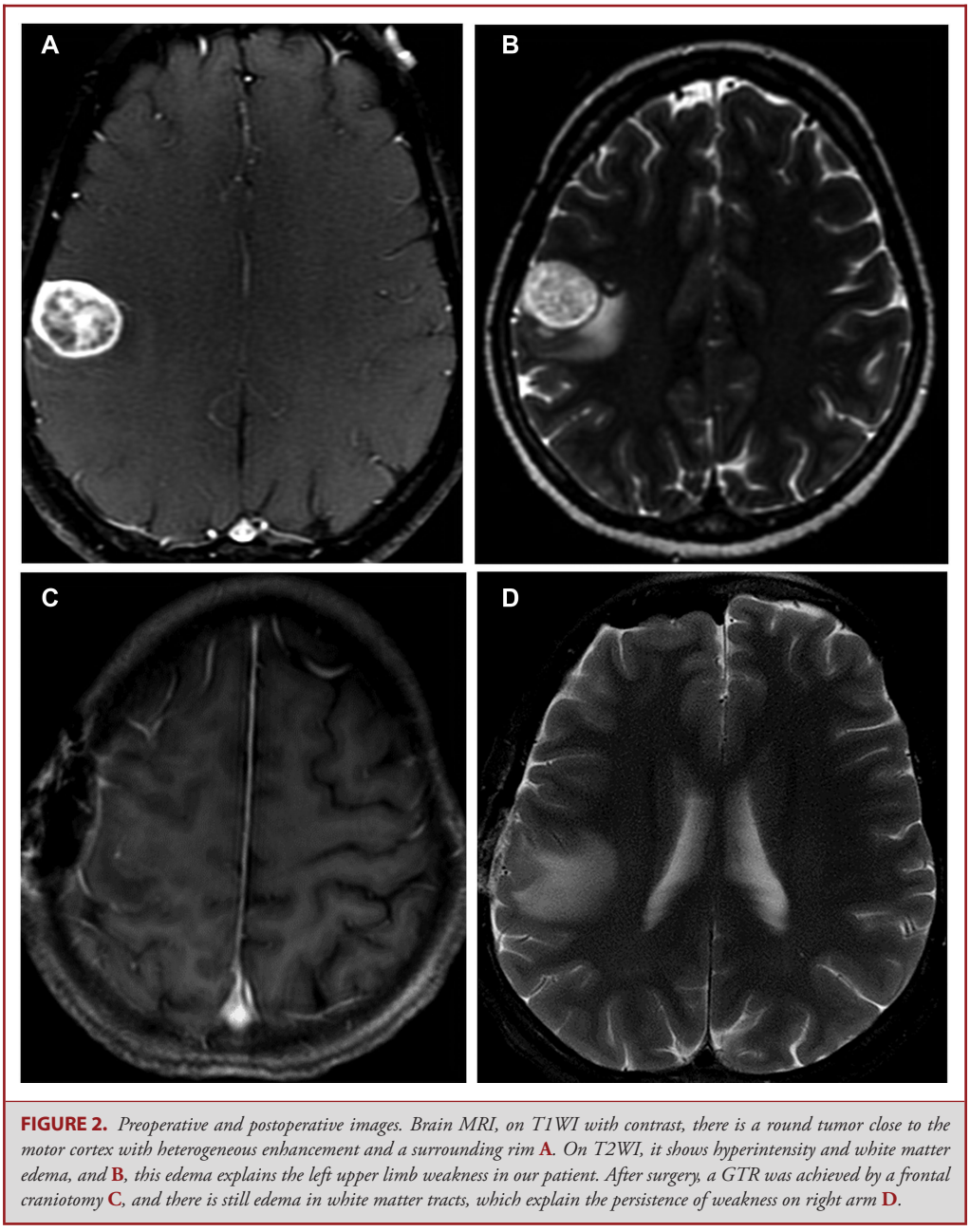

FIGURE 2. *Preoperative and postoperative images. Brain MRI, on T1WI with contrast, there is a round tumor close to the motor cortex with heterogeneous enhancement and a surrounding rim* **A**. *On T2WI, it shows hyperintensity and white matter edema, and* **B**, *this edema explains the left upper limb weakness in our patient. After surgery, a GTR was achieved by a frontal craniotomy* **C**, *and there is still edema in white matter tracts, which explain the persistence of weakness on right arm* **D**.

team decided to treat this tumor recurrence with a new radiosurgery. The patient tolerated well the procedure and currently is neurologically intact 7 mo after the first brain surgery.

Literature Review

Fifty-four studies met predetermined eligibility criteria and were included for data abstraction (Figure 1). The present study included 55 patients from 1971 to 2020: 29 patients were secondary brain MPNSTs (Table 1) and 26 were primary brain MPNSTs or MINSTs (Table 2). Furthermore, the results from both groups are exposed on a comparative table (Table 3).

Demographics Features

Globally, the mean age was 36.8 ± 23.1 yr, with a male-to-female ratio of 1.4:1. Age analysis demonstrates a prevalence of reported cases between the fifth and sixth decade of life for brain metastasis of MPNST and around the first and fourth decade for MINSTs cases. Statistically, MINSTs appear in a younger

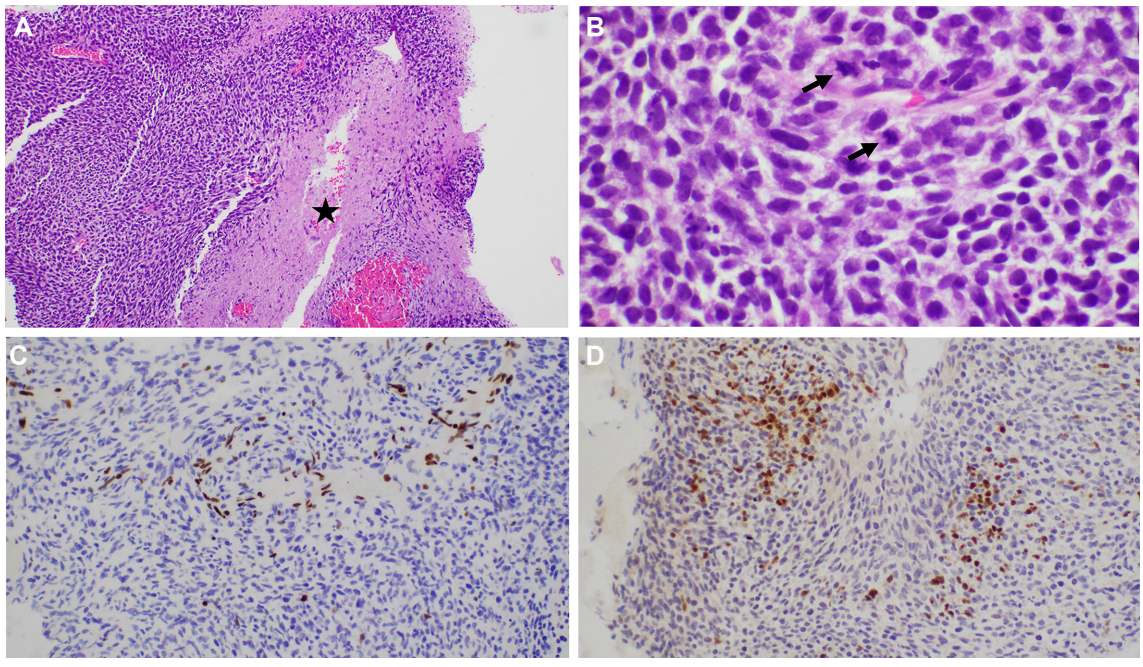

FIGURE 3. *Photomicrograms of surgical specimen.* **A**, *At low magnification (hematoxylin and eosin stain; ×40), the tumor cells are arranged in vague fascicles with multiple foci of necrosis (star).* **B**, *The tumor cells are mostly oval to spindle with very high nuclear: cytoplasmic ratio and numerous mitoses (arrows) (original magnification ×400).* **C**, *H3K27 me3 is lost in tumor cells and retained in the endothelial cells (immunoperoxidase, original magnification ×100).* **D**, *SOX10 is positive in a small percentage of tumor cells indicating neural crest origin (immunoperoxidase, original magnification ×100). The tumor was negative for Melan A, CD34, desmin, SMA, GFAP, and Olig2.*

population compared to brain metastasis of MPNST [t (53) = 1.71, $P = .046$].

Risk Factors Associated to Cerebral MPNSTs

NF is the main risk factor in both types of patients (23% for MINSTs and 27.5% for secondary cerebral MPNSTs, respectively). Radiotherapy was only described in 3 cases[8,22,23] of secondary cerebral MPNST.

A total of 20 patients (77%) with MINSTs and 18 patients (62%) with secondary MPNSTs did not have any associated risk factor.

Primary Site of Secondary Cerebral MPNST

Fourteen patients (48%) had PS-MPNSTs close to the dural sac. One in a cervical nerve,[24] another in a thoracic nerve,[25] and the remainder were located in the lumbosacral plexus.

A total of 15 cases were nonparaspinal (52%), and among them, 8 cases were reported in the limbs, 5 in the trunk, and 2 in the head.

All the secondary MPNST had a clear primary tumor in the body at the time of diagnosis. Even the patients with cerebral involvement at presentation had a primary tumor discovered with a whole-body MRI,[26] spine MRI,[27] or PET scan.[28]

Time to Develop a Brain Metastasis Is Associated to Primary MPNST Site

Three cases had a brain tumor as the initial finding.[26-28] The remaining 26 patients presented with brain involvement from 2 to 180 mo after the diagnosis of an MPNST. The median of time interval was 13.5 mo (Interquartile Range = 18.5 mo).

The period required to develop a brain metastasis from an MPNST (Figure 5) was longer in the group of NPS-MPNST compared to PS-MPNST (U = 46, $P = .025$, Z-score = 1.95).

Location Site of the Brain Tumors

Twenty reported MINSTs were supratentorial (77%), and 6 were infratentorial (23%). Among the supratentorial group, 13 were in the frontal lobes.

Regarding the secondary MPNSTs, the brain locations were not reported in 4 cases.[29-32] In the remaining cases, 16 were supratentorial (64%), 8 were infratentorial (32%), and 1 (4%) had metastases in both the regions.[33]

A total of 7 out of 8 cases of the infratentorial metastases were from PS-MPNSTs (87.5%), and 11 out of 16 cases of the supratentorial group arose from NPS-MPNSTs (69%). Infratentorial metastases are more common than supratentorial metastases in the group of PS-MPNSTs ($P = .027$).

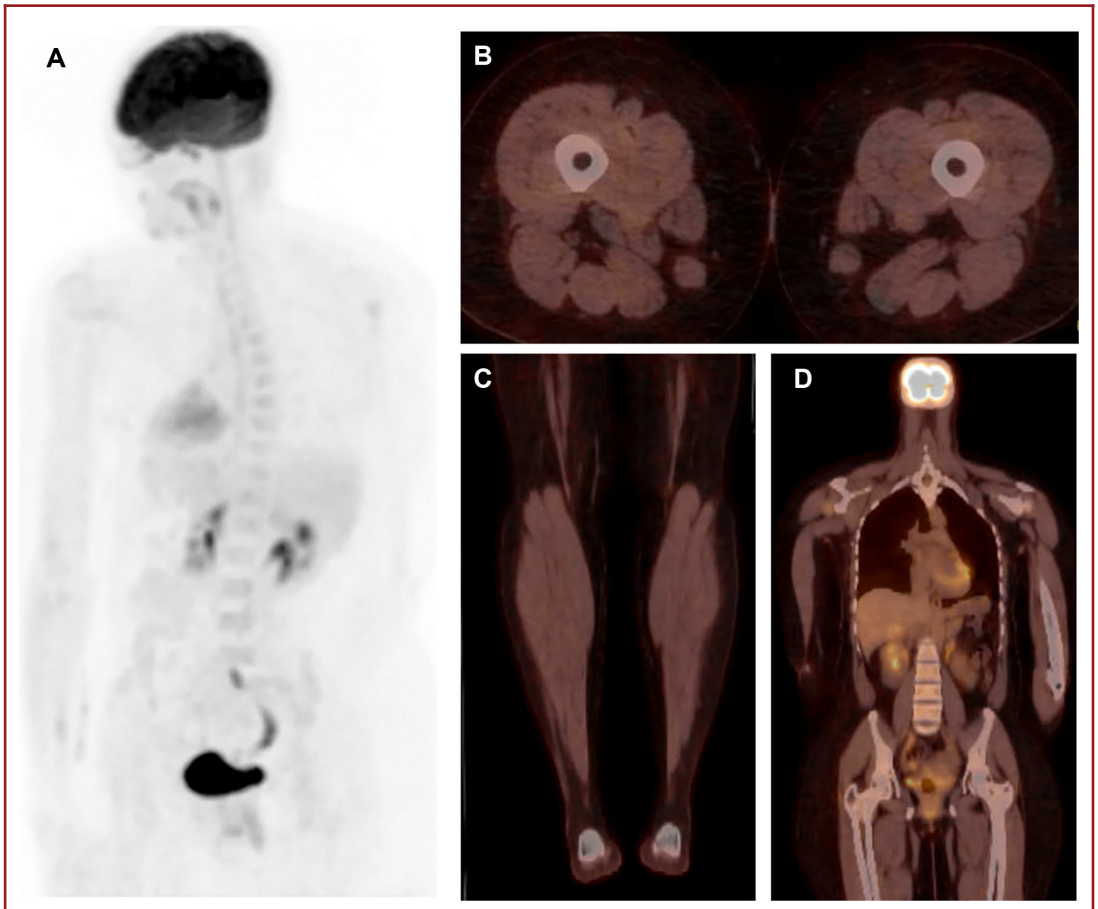

FIGURE 4. *FDG-PET-CT scan. There are no metabolically active lesions involving sacrum or spine on maximum intensity projection images* **A**. *Limbs are a frequent primary site of MPNST, performing fused images with CT from head to toes; we found that the limbs* **B** *and* **C**, *chest, and abdomen* **D** *were clear without metabolically active lesions.*

Treatment Modality Applied in Primary Cerebral MPNST

According to this review, 17 MINST patients received surgery combined with any sort of adjuvant therapy (65.3%), 7 received surgery alone (27%), and 2 were treated with adjuvant therapy after a tumor biopsy (7.7%). GTR was achieved in 16 cases. On the other hand, STR and biopsy were reported in 8 and 2 cases, respectively. Using stratified log-rank test to compare survival in GTR group vs STR/biopsy group (Figure 6A), we found a statistical longer survival time in patients treated with GTR vs STR or biopsy (21.4 ± 19 vs 11 ± 13.5 mo; $P = .009$). Radiotherapy was the most frequent adjuvant therapy applied (69%, n = 18). Adjuvant chemotherapy was used in 7 cases (27%), and only one case received an anthracycline-based regimen.

We did not analyze the impact of treatment modality in the secondary cerebral MPNST because the overall prognosis and survival in this group of patients is determined by the primary disease and the involvement of major organs. In this group, 10 patients were treated conservatively (34.5%), 12 were surgically treated with or without adjuvant therapy (41.4%), and 7 received only adjuvant therapy (24.1%). Adjuvant chemotherapy was used in 4 cases (13.8%), and 2 of them were anthracycline-based regimens.

Survival Since Intracerebral Involvement

In the MINSTs group, 2 articles did not report the survival time or status of the disease during last follow-up.[34,35] In the other 24 patients, the median survival time was 11 mo.

On the other hand, the median survival time of patients with secondary cerebral MPNSTs was 5 mo. After using the Kaplan-Meier procedure (Figure 6B), the survival is statistically longer in patients with MINSTs compared with secondary cerebral MPNSTs ($P = .002$).

Immunohistochemistry

Immunohistochemistry information was not available in 1 (3.8%) MINSTs and in 8 (27.6%) secondary brain MPNSTs.

TABLE 1. Secondary Cerebral MPNSTs

Author	Age and sex	Primary site of MPNST	Treatment for brain metastasis	Risk factor	Interval to BM (mo)	Location of BM (mo)	Time to death from diagnosis of BM (mo)	Overall survival (mo)	Immunohisto-chemistry
White[38]	20, M	Lumbar plexus	None	NF 1	7	Medulla oblongata	1	8	NA
Macaulay[39]	18, M	Right braquial plexus	None	NF 1	2	Bifrontal	1	2	NA
Doi[33]	23, M	Chest	Subtotal Resection (STR) (cerebellar mets)	NF 1	18	Two in cerebellum, four in hemispheres	3	21	NA
Hasegawa[40]	51, M	Cauda equina	STR	NF 1	3	Silvian fissure	1	3	NA
Hirose[41]	52, M	Paraspinal T11 to L2	GTR + RT	None	15	Right parietal lobe	5 (still alive)	20 (still alive)	EMA+, vimentin+, S100–, desmin–
Valdueza[24]	47, M	C3 nerve	None	None	13	Middle fossa	7	20	S100+
D'angelo[42]	68, F	Right forearm	GTR	None	23	Right parietal lobe	13	36	S100+, CK–
Seppala[30]	13, M	Lumbar plexus	None	NF 1	2	NA	2	4	S100–, GFAP–, vimentin+
Fenzi[7]	45, F	Left braquial plexus	None	Previous RT for H lymphoma	18	Right parietal lobe	1	19	S100–, actin–, GFAP–, vimentin+
Haisa[43]	58, F	Maxillary sinus	GTR	None	180	Left temporal lobe	1	181	S100+, desmin–, myoglobin–, EMA-
Oishi[11]	48, M	Abdominal wall	GTR	None	61	Right frontal lobe	2	63	S100+, desmin–, myoglobin–, EMA–
Yone[44]	4, M	Cauda equina	RT + CTX (Vinblastine/ actinomycin-D/ bleomycin/ cyclophosphamide/ cisplatin)	None	7	Cerebellum	14	21	S100+, vimentin+
Tsuchiya[32]	84, F	Right medial orbit	None	None	13	NA	5	18	S100+, vimentin+
Van Eck[45]	83, M	Penis	STR + RT (SRS)	None	91	Left frontal lobe	14	105	S100+, vimentin+
Tilgner[26]	60, M	Sciatic right	GTR + RT	None	0	Bi frontal	11 (still alive)	11 (still alive)	S100+, vimentin+, HMB45+, GFAP–
Park[28]	21, M	Chest wall	GTR + RT + CTX (ifosfamide, mesna, cytoxan, vincristine, doxorubicin)	None	0	Right frontal lobe	9	9	S100+, vimentin+, desmin–
Flannery[31]	34, F	Sciatic nerve	GTR + RT (WBRT + SRS)	NF 2	36	NA	12	48	NA
Xu[46]	8, M	Cauda equina	RT	None	14	Right CP angle	2	16	S100–, EMA–, GFAP–, vimentin+
Stark[8]	56, F	Left sacral plexus	RT	Previous RT for NHL	19	Brain stem	5	24	NA
Park[6]	18, M	Left L2 nerve	CTX (not specified)	None	6	Brain stem	5	11	S100+
Roopesh Kumar[25]	42, M	Left D7 nerve	RT	Immunosuppression (HIV)	4	Right occipital and left temporal lobes	18 (still alive)	22 (still alive)	NA

TABLE 1. Continued

Author	Age and sex	Primary site of MPNST	Treatment for brain metastasis	Risk factor	Interval to BM (mo)	Location of BM (mo)	Time to death from diagnosis of BM (mo)	Overall survival (mo)	Immunohisto-chemistry
Li[47]	33, F	Cauda equina	None	None	16	Brain stem	23	39	S100+, GFAP+, vimentin+, EMA–
Thomas[27]	49, M	Cauda equina	STR	None	0	Left temporal lobe	2	2	S100+, GFAP+, vimentin+
Lau[23]	43, M	Sacral plexus	None	Previous RT for seminoma	54	Medulla oblongata	6	60	S100+, GFAP–
Wu[29]	9, F	Cauda equina	None	NF 2	9	NA	3	12	S100+, vimentin+, HMB45–, EMA–
Hagi[49]	81, F	Left braquial plexus	None	None	11	Medulla oblongata	1	12	S100–, EMA–
Puffer[50]	56, M	Sciatic MPNST	Biopsy + RT	None	32	Right frontal lobe and cauda equina	3	35	NA
Fenlon[85]	40, M	Mediastinum	RT (SRS) + immunotherapy	None	13	Right parietal lobe	11 (still alive)	24 (still alive)	S100+
Purkayastha[51]	48, F	Left thigh	RT + CTX (ifosfamide/doxorubucin/mesna)	None	6	Multiple and sphenoid bone	1	7	S100+, EMA+, vimentin+, desmin–, HMB45–

BM, brain metastasis; CTX, chemotherapy; EMA, epithelial membrane antigen; GFAP, glial fibrillary acid protein; GTR, gross total resection; NA, not available; NF, neurofibromatosis; NHL, non-Hodgkin lymphoma; RT, radiotherapy; SRS, stereotactic radiosurgery; STR, subtotal resection; WBRT, whole brain radiotherapy.

Although there was a difference in the percentage of positivity of some immunomarkers (Table 3), the used immunomarkers were not the same in each report. That is to say, not all the authors reported the same immune markers.

When the marker status was not available, we could consider that the marker was negative, or it was not used for the diagnosis. The only protein reported with consistency was the S-100 status, but we did not find strong evidence to support a prevalence of S-100 in MINSTs or secondary cerebral MPNSTs (S-100, $P = .13$).

DISCUSSION

Even though extracranial MPNSTs are very rare with an incidence of around 0.001%,[36] the intracranial counterpart is even more uncommon. The intracranial tumors could be divided into 2 groups: extra-axial and intraparenchymal lesions.[14] We have achieved a comprehensive review of all the exceedingly rare published cases of MPNSTs inside the brain.

Similar to others brain tumors, these tumors can be secondary or primary tumors. According to our analysis, all the secondary tumors had a primary extracranial lesion at the time of diagnosis of the cerebral involvement. This finding helps us to classify a tumor as a primary cerebral MPNST when we have a patient with a cerebral MPNST (like our reported case) and negative screening tests, like CT scan, PET scan, and/or whole body MRI. The term MINST was first introduced by Barnard in 2011[37] and, in our opinion, represents a better way to anatomically describe these tumors. MINSTs are not a metastatic lesion from a primary disease, and the overall survival is significantly different (Figure 6B).

The phenomenon of brain metastasis from an MPNST is an exceedingly rare occurrence and expected length of survival is even shorter (median SSII was 5 mo).[17,26] According to our literature review, there are 29 previously reported cases of MPNST with brain metastases.[6,8,11,22-26,28,29,30-33,38-43,44-51] The metastatic pathways to the brain with regard to the primary sites of MPNST are direct invasion, cerebrospinal fluid (CSF) dissemination, and hematogenous metastases.[28] A greater potential for brain metastasis may exist from PS tumors,[12] and our analysis confirmed a shorter mean time for spreading to the brain in this group (13 ± 13.5 mo compared to 38.8 ± 49 in NPS tumors; $P = .025$), and the most common site of metastasis was the infratentorial region ($P = .027$). Most of the PS-MPNSTs in our series had an intradural component without metastases outside the central nervous system,[8,28,29,44,46,48] suggesting that CSF dissemination is the most common pathway for brain involvement.

In MINST patients, the situation is completely different. This is an intracerebral tumor from a peripheral nervous system component. MINSTs could be considered the malignant

TABLE 2. Primary Cerebral MPNSTs or MINSTs

Author	Age and sex	Location of MINST	Treatment	Risk factor	Overall survival (mo)	Immunohistochemistry
Bruner[71]	18, M	Frontal lobe	GTR	None	66	S100+, GFAP+
Stefanko[72]	15, M	Left parietooccipital lobe	GTR + RT + CTX (cisplatin)	None	9	S100+, GFAP–, desmin–, myoglobin–
Singh[73]	61, F	Right cerebellar	GTR + RT	None	18	S100+, GFAP–, desmin–, actin–
Jung[74]	40, M	Right atrium	STR + RT	None	7	S100+, vimentin+, GFAP–, EMA–
Sharma[75]	8, F	Right temporal lobe	GTR + RT	None	17 (still alive)	S100+, GFAP–, EMA–, myoglobin–
Takahashi[76]	57, M	Left atrium	STR + CTX (carboplatin)	NF1	4	S100+, GFAP–
Tanaka[56]	4, F	Right parietooccipital lobe	GTR	None	19 (still alive)	S100+, vimentin+, GFAP–
Bornstein-Quevedo[57]	3, M	Right parietooccipital lobe	STR	None	1	S100+, desmin+, Myoglobin+, GFAP–, EMA–
Maiuri[58]	29, F	Cerebellar vermis	GTR + RT	None	8	S100+, GFAP–, myoglobin–, desmin–
Beauchesne[59]	35, M	Brain stem	Biopsy + RT + CTX (doxorubicin)	None	29	S100+, GFAP–, EMA–, vimentin–
Cauwer[60]	57, M	Right frontal lobe	GTR	NF1	5	S100+, desmin+, vimentin+
Oztanir[70]	1, F	Right frontal lobe	STR	NF1	2	S100+
Kozic[34]	39, M	Brain stem	Biopsy + RT	None	NA	S100+
Scheithaue[61]	69, M	Right frontal lobe	STR	None	4	S100+
Barnard[37]	75, F	Left frontal lobe	GTR + RT	None	26 (still alive)	S100+, vimentin+, GFAP–, desmin–, EMA–
Munckhof[62]	6, F	Left frontal lobe	GTR + RT + CTX (Ifosfamide, carboplatin, etoposide)	None	48 (still alive)	S100+, vimentin+, GFAP–
Gong[63]	55, F	Brain stem	GTR + RT	None	5 (still alive)	S100+, desmin+, myoglobin+, GFAP–, EMA–
Smith[64]	26, M	Bifrontal	STR + RT + CTX (ifosfamide/carboplatin/ etoposide)	NF1	13	S100–, GFAP–, desmin+, myoglobin+
Shweikeh[15]	18, M	Right frontoparietal lobe	GTR + RT	NF1	52	S100–, desmin+, GFAP–, actin–, EMA–, myoglobin–
Fevre[65]	47, F	Right frontal lobe	GTR + RT	None	20	S100+, GFAP+, desmin–, myoglobin–, EMA–
Lafay-Cousin[66]	11, F	Right frontal lobe	STR + RT + CTX (Ifosfamide, carboplatin, etoposide)	NF1	38 (still alive)	NA
Abdolkarimi[35]	4, F	Left frontal lobe	GTR + RT + CTX (vincristine/actinomycin-D/Ifosfamide/Mesna	None	NA	S100+, GFAP–, EMA–
Son[67]	50, M	Right frontal lobe	GTR + RT	None	13 (still alive)	S100+, GFAP–
Baharvahdat[69]	3, M	Spine	STR	None	1	S100+, vimentin+, GFAP–, EMA–, HMB45–
Arumugam[68]	44, F	Left parietal lobe	GTR + RT	None	9 (still alive)	S100+, vimentin+, GFAP–, EMA–
Presented case	38, F	Right frontal lobe	GTR + RT	Prior RT for breast cancer	6 (still alive)	S100+, SOX10+, EMA+, GFAP–

BM, brain metastasis; CTX, chemotherapy; EMA, epithelial membrane antigen; GFAP, glial fibrillary acid protein; GTR, gross total resection; NA, not available; NF, neurofibromatosis; RT, radiotherapy; STR, subtotal resection.

TABLE 3. Comparative Results From Primary and Secondary Cerebral MPNSTs

Variables	Type of intracerebral MPNST (%)	
	Primary or MINST	Secondary
Age (yr)	31.2 ± 23	41.8 ± 22.4
Number of patients (N)	26	29
Male	13 (50%)	19 (65.5%)
Female	13 (50%)	10 (34.5%)
Risk factors		
NF	6 (23%)	8 (27.5%)
Previous radiotherapy	0 (0%)	3 (10.5%)
None	20 (77%)	18 (62%)
Primary site of secondary MPNST		
Paraspinal	–	14 (48.3%)
Cervical	–	1 (3.5%)
Thoracic	–	1 (3.5%)
Lumbosacral	–	12 (41.4%)
Nonparaspinal	–	15 (51.7%)
Time to develop a brain metastasis		
Paraspinal (mo)	–	13 ± 13.5
Nonparaspinal (mo)	–	38.8 ± 49
Brain location of the tumors		
Supratentorial	16 (55.1%)	20 (77%)
Infratentorial	8 (27.6%)	6 (23%)
Not available	5 (17.3%)	0 (0%)
Treatment modality		
GTR + RT/CTX	13 (50%)	4 (13.8%)
STR + RT/CTX	4 (15.4%)	1 (3.5%)
Biopsy + RT/CTX	2 (7.7%)	1 (3.5%)
Adjuvant therapy alone	0 (0%)	7 (24.1%)
GTR	3 (11.5%)	3 (10.3%)
STR	4 (15.4%)	3 (10.3%)
None	0 (0%)	10 (34.5%)
Median survival since intracerebral involvement (mo)	11	5
Immunohistochemistry		
IH available	25 (96.2%)	21 (72.4%)
S-100+	23 (92%)	16 (76.2%)
Vimentin+	7 (28%)	13 (62%)
Desmin+	5 (20%)	0 (0%)
GFAP+	2 (8%)	2 (9.5%)
Myoglobin+	3 (12%)	0 (0%)
EMA+	1 (4%)	2 (9.5%)
HMB45+	0 (0%)	1 (4.8%)
IH not available	1 (3.8%)	8 (27.6%)

CTX, chemotherapy; EMA, epithelial membrane antigen; GFAP, glial fibrillary acid protein; GTR, gross total resection; NF, neurofibromatosis; RT, radiotherapy; STR, subtotal resection.

counterpart of the well-known intracerebral schwannomas.[52-54] The origin of these peripheral nerve tumors may be in the nervi vasorum. The nervi vasorum are perivascular autonomic nerves from the peripheral nervous system within the adventitial layer of large and small pial arteries. Therefore, they are considered "extrinsic" in nature.[55] We found 26 cases of MINSTs (including our reported case).[15,34,35,37,56-76] The age of presentation was significantly younger compared with the metastasis, with most of the cases reported during childhood and early adulthood ($P = .046$). The age and the absence of a primary tumor at the moment of the diagnosis are helpful tools to conduct the diagnosis to an MINST instead of a cerebral metastasis from a primary MPNST.

In general terms, the management of MPNST is a clinical challenge. However, surgery is the mainstay of treatment, and radiotherapy provides local control with little effect on long-term survival rates.[9,77,78] In general, MPNST has a 5-yr survival rate of only 64%.[26] GTR is not always feasible and ranges from 20%

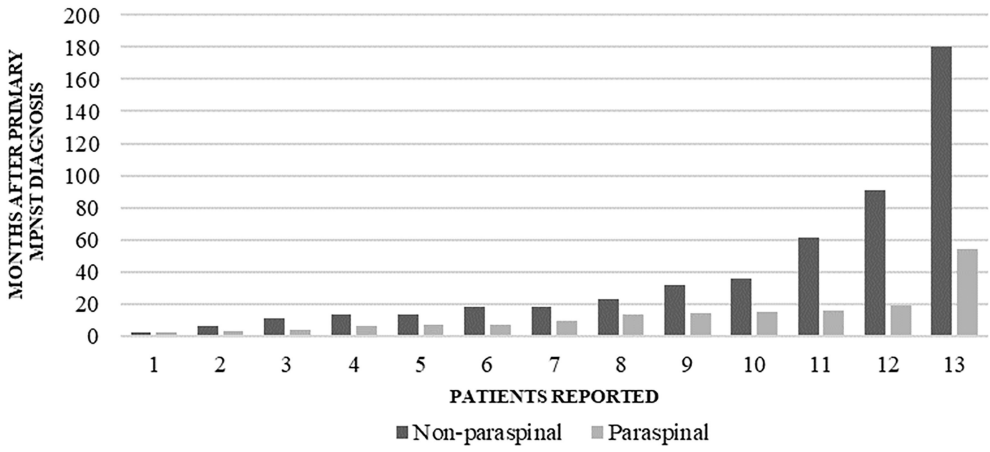

FIGURE 5. *Time interval from primary diagnosis to brain metastasis reported in PS-MPNST and NPS-MPNST patients.*

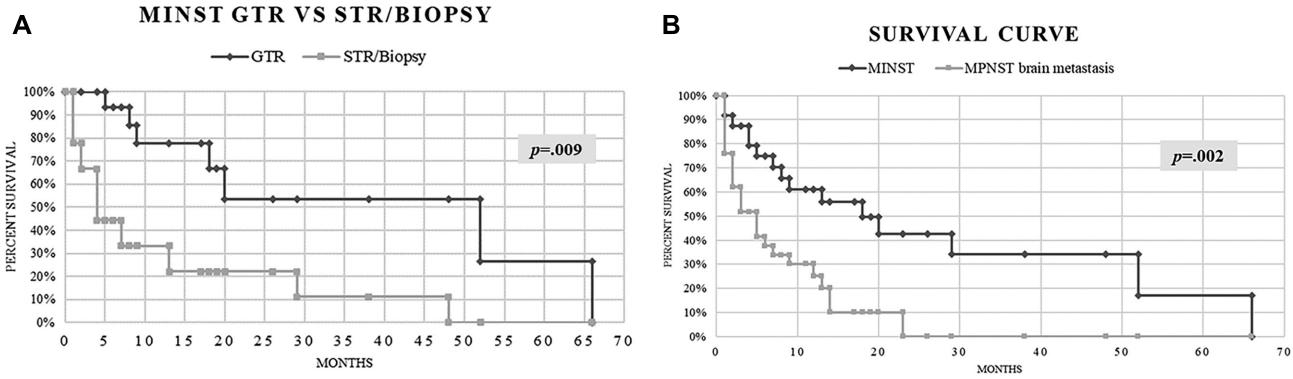

FIGURE 6. *Survival analysis of MINST treated with GTR vs STR/biopsy* **A**. *There is a statistically longer survival in patients who received GTR over STR or biopsy. The 2-yr survival rate in GTR was 53% vs 22% in STR or biopsies (P = .009). Overall SSII* **B**. *The 2-yr survival rate was 0% in secondary cerebral MPNSTs vs 43% in MINST patients (P = .002).*

in PS-MPNSTs to 95% in tumors in extremities.[77] The brain is not the exception to this rule. GTR in MINSTs was only achieved in 61.5% (16/26) of the cases with a clear benefit in survival compared to STR or biopsies. The 2-yr survival rate in GTR was 53% vs 22% in STR or biopsies ($P = .009$). For MPNST of peripheral location, negative surgical margin is the most significant prognostic factor for survival and local control of the disease.[79] Negative margins are often not feasible in the brain because of proximity to eloquent areas such as the primary motor cortex, so radiotherapy is used in most of the reported cases.

On the other hand, for secondary cerebral MPNSTs the prognosis is worse because the involvement of the brain is a sign of advance disease stage. Treatment of these metastases varies widely from en bloc surgical resection followed by whole brain radiotherapy[12] to palliative care given in cases of widely metastatic disease. Evidence for any relevant cytotoxic effect of chemotherapy is not available.[80] In our review, 10 patients were treated conservatively (34.5%), 12 were surgically treated with or without adjuvant therapy (41.4%), and 7 received only adjuvant therapy (24.1%). Despite the aggressive treatment, prognosis is worst in this group with a 2-yr survival rate of 0% vs 43% in MINST patients ($P = .002$).

With such a rare clinical entity as MPNST, the pathologist must complete a very thorough analysis to ensure a correct diagnosis. The combination of malignant histology features and immunohistochemistry is mandatory; the diffuse expression with either S-100 or SOX10 would strongly suggest cellular MPNST.[81] A negative Melan A, desmin, and GFAP/Olig2 almost rule out melanoma, rhabdomyosarcoma, or a primary glioma, respectively.[82-84] Sometimes, when the cell features are very

undifferentiated and primitive, molecular analysis and the clinical context must be kept in mind.[64] According to our review, immunohistochemistry has been reported in a very heterogeneous way (Table 3), showing the need of a global database. The proteins S-100 and vimentin were the 2 most reported proteins, but only S-100 was statistically analyzed, and we did not find any difference in the positivity of S-100 in both types of tumors ($P = .13$). Interestingly, in the MINST group there were 5 triton tumors, a subgroup of MPNST with focal rhabdomyoblastic differentiation.[57,60,63,64,76]

Limitations

In summary, our systematic review provides a comprehensive analysis of a very rare peripheral nerve pathology inside the brain. The main question will always be if the tumor is a primary brain tumor or a brain metastasis, and our analysis could be very helpful to answer this question, but it is worth mentioning that our study has several limitations. Among them are biases inherent to retrospective studies. At the same time, the diagnosis and treatment for the extracranial and intracranial MPNSTs has improved over the last decades, and these improvements could have affected the prognosis and survival between the patients included in this study. Finally, because of the statistical oddity of MINSTs, there is no prospective study, and the creation of a global database could be very helpful in the management of these patients.

CONCLUSION

MPNST is a very aggressive cancer with high metastatic potential, including the brain, but primary cerebral occurrence is also possible. The preferred way to describe a primary cerebral MPNST is with the name MINST because the survival and prognosis are slightly better. If the whole-body screening studies do not show a primary tumor site, our findings support that this indicates a diagnosis of MINST instead of cerebral MPNST metastasis. Correct pathological diagnosis and early treatment of MPNSTs represent the best opportunity for increasing overall survival in this highly malignant disease.

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COMMENT

The authors present a case report of a primary intracranial MPNST and reviewed the literature of the tumors currently classified as MPNST tumors by the latest 2016 *WHO Classification of Tumours of Nervous System* that had intracranial presentation. As the authors note, these tumors are extremely rare. Eligible cases were reported in the literature from 1971 to 2020 and the authors should be commended for their effort in finding 54 cases that met their eligibility criteria for the literature review and data collection. They distinguish secondary from primary intracranial MPNSTs and analyze various features in well-presented Tables and Figures. As expected, metastatic MPNST tumors have a much worse prognosis than primary tumors, and although there is insufficient data to make definitive statement, this paper makes a good case that the current WHO classification of MPNST is imprecise. Their data suggests that we are dealing with at least 2 different type of tumors, according to their behavior. They propose reverting to the nomenclature of primary intracranial MPNST as MINST (malignant intracerebral nerve sheath tumor). Finally, they correctly state that a global tumor bank of these MPNST would allow a modern genetic profiling of MPNSTs and help to establish a more precise molecular and pathological classification for tumors currently grouped as MPNSTs.

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