Review

Primary Central Nervous System Melanoma (pCNSM) and Treatment Protocols: A Literature Review

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Abstract: Background: Melanocytes, responsible for melanin production, originate from the neural crest and can give rise to malignant tumors known as melanoma. Primary Central Nervous System Melanoma (pCNSM) is rare, with an incidence of 0.005 cases per 100,000 individuals annually. Considering its rare occurrence and the variations in tumor biology, a comprehensive treatment strategy has not yet been introduced. Immunotherapy is an emerging treatment avenue warranting further exploration. **Objectives:** In this review, we conducted an extensive literature review on patients with pCNSM, including the brain and spine, to determine the characteristics and most successful treatment protocol for pCNSM. **Materials and Methods:** A review of all published articles from 1980 to 2023 was done including PubMed and Google Scholar articles, multiple published case studies, and the Archives of the American Institute for Radiologic Pathology. **Results:** During our review we found 138 articles with 148 pCNSMs (77 cases of brain and 71 cases of spinal primary melanoma) spanning from 1980 to 2023. The vast majority of patients (95%) underwent therapeutic gross total or partial resection of the tumors followed by radiotherapy. Only two cases with brain melanomas underwent immunotherapy. The treatment strategies of primary brain melanomas were similar to those of primary spinal melanoma (PSM) but exhibited better outcomes in PSM cases. **Conclusion:** Our findings suggest surgical intervention, followed by adjuvant radiotherapy + immunotherapy, yields favorable outcomes in PSM cases but not in primary brain melanomas. Further multicentric studies are needed to explore alternative, more effective treatment modalities.

Keywords: brain neoplasms; spinal neoplasms; melanoma

Introduction

Malignant melanoma is broadly initially reported in skin and mucus membranes, rarely presenting elsewhere, particularly in the brain and spinal cord. According to the neurogenic theory, the melanocytic element originates from the neural crest, which also gives rise to the lepromengial tissues and develops into the mesoderm, forming this tumor. Other theories, such as mesodermal and ectodermal, are also mentioned, discussing the origin of this pigment. A hypothesis highlights the probability of melanization of benign structures, such as schwannomas, gliomas, and melanocytic meningiomas, as well as meningeal melanocytosis [1]. In 2007, the World Health Organization sub-classified primary melanocytic lesions into four groups. The malignant melanoma classification comprises primary cerebral malignant melanoma (PCMM) [2]. Melanocytic lesions of the CNS are either low-grade (melanocytoma), intermediate-grade, or high-grade (melanoma). In 1976, Hayward proposed this classification: (I) Primary brain melanoma, (II) Secondary brain melanoma, and (III) other tumors. He further noted that the diagnosis is based on the absence of melanoma outside the CNS and in other sites in the CNS, in addition to histological confirmation of melanoma [1,3]. PCM varies based on the position and characteristics of the tumor. Virchow illustrated the first PCM case, primary diffuse intracranial malignant melanoma, in 1859 [4]. Ogle displayed the first case of primary

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solitary intracranial melanoma in the pineal gland [5]. However, a digital copy is not available for both. A Foot et al. 1931 publication is the oldest to be found as an electronic version [6].

Despite improvements in medical science, the exact mechanisms of PCM's invasiveness remain unclear. Its invasiveness may be due to its high degree of similarity to vessel surface molecules, a property that distinguishes it from other melanomas [7]. The diagnosis of this sporadic tumor relies on the exclusion of metastatic skin melanoma and limiting proposed differentials according to the pathology reports to confirm the diagnosis. PCNSM is a life-depleting and, in some cases, threatening disease. Close to 50% of patients from earlier case reports have expired within 2.5 years. Patients with skin melanomas may reveal 6 to 11% metastasis in the CNS, and this percentage may increase up to 90% in autopsies. Accordingly, it is necessary to determine whether it is primary or secondary metastatic, as treatment and prognosis vary. Based on our review, we seek to aid physicians with the appropriate clinical approach to similar cases in this rare condition by incorporating appropriate treatment plans. It may also be a valuable resource for those interested in expanding their research or teaching in melanoma treatment. The results can offer a foundation for the creation of creative treatment plans for medical technology designers and developers, which can lead to more effective and efficient treatment methods.

Methods

For our literature review, we used data from various open-access and subscription journals, and full-text case reports, published in or translated into English, documenting patients with confirmed PCM through biopsy or surgical histopathology. We also reviewed electronic medical records, multiple published case studies, and the Radiologic Pathology Archives of the American Institute for Radiologic Pathology.

The literature emphasized cases reported from 1980 to 2023 without restrictions on gender, age group, or ethnicity. Studies where patients had at least one follow-up visit and/or imaging conducted after a variable duration from the initiation of treatment were considered.

A search through main literature search engines like the PubMed database was done using a MESH strategy with the following terms: "Brain Neoplasms"[Mesh], "Melanoma"[Mesh], "Spinal Neoplasms"[Mesh], and "Meningeal Neoplasms"[Mesh]. Case reports, systematic reviews and/or meta-analyses, and clinical trials involving the testing of drugs and/or surgical techniques were studied extensively. Some of the studies did not meet the criteria established for this study [8–10]. Subsequently, an advanced search on the Cochrane Library identified one review and 31 trials for PCM and PSM; however, these sources did not provide relevant data needed for this review.

A search on Google Scholar for PCM and PSM yielded 148,000 and 118,000 articles respectively although on final scrutiny only 23 articles were found relevant to our review.

Articles other than English languages were not reviewed. Case reports presented in congresses, under peer review, or as abstracts, published English full-text case reports of patients with missing data or not meeting the criteria for PCM and PSM diagnosis were left out. Also, studies where PCM and PSM patients who did not receive any treatment, possibly due to death before treatment initiation or a lack of medical attention were not included [11–18]. As a result,118 case reports from PubMed-indexed journals and 21 case reports from other journals were excluded.

Case reports were also independently reviewed and the reviewed studies were arranged into tables.

Results

We comprehensively reviewed 138 articles involving 148 patients with PCNSM from 1980 to 2023. The age range of these patients varied from 6 years and 8 months to 82 years, with an overall mean age of 45.98 years. Notably, there was a male predominance, with 81 male patients compared to 67 female patients among all pCNS melanoma cases.

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When examining primary intracranial malignant melanoma (PIMM) specifically, we identified 73 reported articles with 77 patients, of which 40 were male and 37 were female. The mean age among PIMM patients was 42.75 years. In contrast, PSM showed a significant gender difference, with 41 male and 30 female patients and a mean age of 50.7 years. Regarding the location of the tumor within the CNS, tumors were found in various brain lobes, including the frontal lobe (19.5%), temporal lobe (12%), parietal lobe (10.4%), frontoparietal lobe (1.3%), temporoparietal lobe (Insular) (2.6%), occipital lobe (3.9%), and parieto-temporal lobe (1.3%). Collectively, these lobes accounted for 51% of all PIMM cases. Other areas affected included the fornical callosum (1.3%), cavernous sinus (1.3%), intra and suprasellar region (2.56%), pineal gland (10.4%), pons (1.3%), cerebellopontine angle (16.9%), cerebellum (3.9%), medulla oblongata (1.3%), involvement of more than one lobe (6%), and other structures (5%).

The most common treatment approach for PIMM involved a combination of surgical intervention and adjuvant postoperative radiotherapy, accounting for 69.2% of all treatments. Unfortunately, death was the clinical outcome for 36.3% of PIMM patients, while 32.5% achieved complete remission (no evidence of disease).

For studies regarding PSM, cervical vertebrae were affected in 33.8% of cases (n=24), primarily in males (n=15), with a mean age of 46. Thoracic vertebrae were affected in 36.6% of cases (n=26), with a male-to-female ratio of 7:6 and a mean age of 50. Adjuvant postoperative radiotherapy was commonly recommended for thoracic PSM (38.4%), resulting in a 50% complete remission rate but also a high recurrence rate. Lumbar vertebrae PSM accounted for 11.3% (n=8) of cases, primarily affecting females with a mean age of 60. In this group, surgical intervention was the most common treatment modality (62.5%), and half of the patients achieved no evidence of disease. Sacral vertebrae PSM was the least common, accounting for 2.8% (n=2) of cases, all male, with a mean age of 22.5. These patients achieved complete remission upon receiving adjuvant post-operative chemotherapy and radiotherapy. Another group of patients presented with multiple spinal cord lesions or diffuse leptomeningeal disease (15.49%), with equal gender distribution and a mean age of 52 years. Treatment approaches varied, and these patients had a complete recovery rate of 36.4% but also a death rate of 27.2%.

In total, PIMM patients received mainly adjuvant post-operative radiotherapy or surgical intervention alone, with 36.3% of them ultimately succumbing to the disease. Conversely, 42.25% of PSM patients underwent surgical intervention alone, leading to a cure rate of 57.7%.

To the best of our knowledge, recurrence occurred in 11 patients, four of whom had PCM, including a case of frontal lobe PIMM that experienced two recurrences. Additionally, we identified 14 pediatric cases with PCNSM, spanning infants to adolescents.

Table 1. Clinical characteristics, imaging findings, treatment modalities for PIMM and PSM patients.

Primary intracranial malignant melanoma											
Site	*N0.(%)*	*Mean Age*	*Gender M(n.)/F(n.)*	*Major clinical manifestation*	*Imaging*	*Treatment modality: Number (%)*					
						*Treatment (without surgery)**	*Adjuvant therapy*				*Surgical intervention only*
							*CTx***	*RT*	*IMT*	*Combined therapy*	
Temporal lobe	9(12)	48.2	M(5),F(5)	Headache	MRI :Hyperintense T1, hypointense T2,CT:Hyperdense	_	_	1	_	4	4
Frontal lobe	15(19.5)	41.73333	M(10),F(5)	Headache and Blurring of vision	MRI :Hyperintense T1, hypointense T2,CT:Hyperdense	_	_	6	1	4	4
Parietal lobe	8(10.4)	28.14	M(6),F(2)	Headache and vomiting	MRI:Iso/hyperintinse T1,Hypo /Hyperintinse T2,CT:Hyperdense	–	–	4	_	_	4
Occipital lobe	3(3.9)	40.66667	M(2),F(1)	Diminished vision bilaterally	MRI:Hyperintense T1 , Iso /hypointense T2	_	_	1	_	_	2
Front-parietal lobe	1(1.3)	66	M(1),F(0)	Clouding of consciousness	MRI :Hyperintense T1, hypointense T2	–	–	_	_	_	1
*Parieto-temporal lobe****	1(1.3)	67	M(0),F(1)	Psychomotor agitation, altered consciousness	CT-angiography mass measured (6 cm × 5 cm) with intralesional calcifications	_	_	_	_	_	1
Temporoparitetal lobe (Insular)	2(2.6)	28.5	M(2),F(0)	Impaired vision ,contralateral paresis	MRI:Hyperintense T1 , hypointense T2	–	***1***	_	_	1	_
Cerebellopontine angle	13(16.9)	40.30769	M(4),F(9)	Hearing loss	MRI :Hyperintense T1, hypointense T2	_	_	7	_	1	5

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Cerebellum	3(3.9)	52	M(1),F(2)	Dizziness and gait disturbance	MRI :Hyperintense T1, hypointense T2	–	–	1	–	2	–
Pons	1(1.3)	10	M(0),F(1)	Lethargy	MRI:Hyperintense T2	–	–	–	–	1	–
Forniceal callosum	1(1.3)	51	M(0),F(1)	Headache	MRI :Hyperintense T1, hypointense T2	–	–	–	–	1	–
Cavernous sinus	1(1.3)	36	M(0),F(1)	Incomplete ipsilateral paralysis	MRI :Hyperintense T1, hypointense T2	1	–	–	–	–	–
Pineal gland	8(10.4)	58.66667	M(5),F(4)	Gait disturbances	MRI:Hyperintense T1 , Iso /hypointense T2	2	1	5	–	–	1
Intra and suprasellar	2(2.6)	37	M(0),F(2)	Deterioration of vision	MRI :Signal heterogeneity of the lesion	–	–	1	–	1	–
Medulla oblongata	1(1.3)	40	M(1),F(0)	Vertigo and headache	MRI :Hyperintense T1, hypointense T2	–	–	–	–	–	1
Others*	5(6)	45	M(3),F(2)	Swelling in the head	MRI :Hyperintense T1, hypointense T2,CT: mixed iso/hyperdensity	–	–	1	–	1	3
More than one Structure	3(4)	33.33	M(0),F(3)	Vomiting	Nonspecific	1	–	–	–	1	1
Total	77(100)	42.24	M(40),F(37)	Headache ,Blurring of vision, Vomiting and Gait disturbances	MRI: Hyperintense T1, hypointense T2, CT: mixed iso/hyperdensity	4(5%)	2(3%)	27(34.6%)	1(1%)	17(21.8%)	27(34.6%)

Primary Spinal melanoma

Site	***N0.(%)***	***Mean Age***	***Gender M(n.)/F(n.)***	***Major clinical manifestation***	***Imaging***	***Adjuvant Treatment modality: Number (%)***					
						Treatment (Without surgery)	***Adjuvant Therapy***				***Surgical intervention only***
							CTx	***RT***	***IMT***	***Combined Therapy***	
Cervical vertebrae and CMJ	24(33.8%)	46	M(15),F(9)	Neck pain, quadriparesis	MRI :Hyperintense T1, hypointense T2	–	2(8.3%)	6(25)	–	2(8.3%)	14(58.4%)

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				and Shoulder pain							
Thoracic vertebrae	26(36.6%)	50	M(14),F(12)	Paresthesia and paraparesis of lower limb	MRI :Hyperintense T1, hypointense T2, Spinal Myelography : Complete block of the contrast material	_	3(11.53%)	10(38.4%)	_	6(23.07)	7(27%)
Lumber vertebrae	8(11.3%)	60	M(3),F(5)	Chronic back pain	MRI:Iso,hyperintense T1 , hypointense T2CT: Hyperdense	_	_	1(12.5%)	_	2(25%)	5(62.5%)
Sacral vertebrae	2(2.8%)	22.5	M(2),F(0)	Left posterior hip pain ,Schwannoma or ependymoma	MRI :Hyperintinse T1,heterogenous T2	_	1(50%)	1(50%)	_	_	_
Multiple vertebras	11(15.5%)	52	M(6),F(5)	Quadriplegia	MRI: Hyperintense T1, iso/hypointense T2, Whole-body FDG PET/CT: demonstrated abnormal activity in the cauda equina. 16.2 mCi of FDG was used, and this lesion measured an average standard uptake value of 4.4	_	_	3(27.2%)	_	4(36.4%)	4(36.4%)
Total	71(100%)	49.49	M(40),F(31)	Back neck and shoulder pain, Paresthesia and paraparesis of lower limb	MRI:Hyperintense T1 , hypointense T2 CT: Hyperdense	_	6(8.45%)	21(29.6%)	_	14(19.7%)	30(42.25%)

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Table 3. Characteristic feature and radiological differential diagnosis of pigmented lesion of the leptomeninges.

Differential diagnosis	*Age range*	*Gender*	*Type*	*Pathology (Microscopic)*	*Imaging*		*Treatment*
					MRI	*CT*	
Melanotic meningioma	40-60	Benign affect twice female ,Malignant equal.	Majority Benign	Mild Swirly shape cells, sand bodies easily visible. Positive for EMA ,negative for HMB-45 and Melan-A	T1: iso- or hyperintense ,T2: hypo- or hyperintense	Isodense	Surgical and adjuvant radiotherapy
Malignant melanotic nerve sheath tumours (Melanotic shwannoma)	20-60	Equal	Potentially malignant	Mild and sorted out in a palisade shape, negative for HMB-45 and Melan-A	T1: hyperintense ,T2:hypointinse	Isodense or slightly hyperdense	Complete surgical resection
Meningeal melanocytoma	30-50	Equal	Benign	Uniform cell, small atypia, no hemorrhage and necrosis, mitosis 0 to 1/10HPF, no infiltration in adjacent tissues	T1: isointense or hyperintense T2: isointense or hypointense	Isodense to hyperdense	Complete surgical resection
Primary melanoma	40-50	Male	Malignant		T1:hyperintinse ,T2:hypointinse	Hyderdense	Limited data
Metastatic melanoma (cutaneous origin)	55-65	< 50 Female 65-80 Male	Malignant	Atypia is prominent, necrosis is and the BRAF, NRAS, and KIT gene variants	T1:hyperintinse ,T2:hypointinse	NECT: single to multiple nodules of increased attenuation CECT: well-enhanced lesions	Combination of regional/systemic chemotherapy with associated immunotherapy and/or radiation therapy

Note: CPA: Cerebropointine angle, NECT: non contrast enhanced computed tomography, CECT: contrast enhanced computed tomography

Reference

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Discussion

Intracranial-melanoma-related literature is mainly distributed in countries like Japan, the Eastern United States, and Europe [14]. Suranagi et al. reviewed 19 cases over 25 years and noticed a male predominance, similar to our findings [8]. PCNSM rarely presents with distant metastasis, but reported liver, bone, and lung involvement cases have been found [6,144–147]. As for PCM, Quillo-Olvera et al. expressed their findings on the most common locations of primary brain melanoma, which were the lobe (53.1%), posterior fossa (17.3%), and pineal region (13.6%) [10]. This corresponds with our findings. The most extensive registered study included 81 patients with primary solitary intracranial cerebral melanoma from 1899 to 1992, followed by 54 cases in 2019 and 49 patients between 1993-2017 [16,22,148]. The data shows that thoracic, especially T10–11, had higher recorded figures [147]. This correlates with the findings of Alexander D. Fuld et al., who stated that more than 60% of patients had PSM of the thoracic vertebrae, which aligns with the findings of our study. Another study said that the thoracic segment (42.3%) was the most common, followed by the cervical (34.6%), thoracolumbar (11.5%), cervicothoracic (7.7%), and lumbar (3.8%) segments [148]. On the contrary, one of the rarest forms of PIMM was described in a 66-year-old female diagnosed with primary intracranial leptomeningeal melanomatosis. It is a diffuse variant of PCNSM, where the tumor infiltrates the subarachnoid space and involves the brain's outer surface [148]. A rare case of primary intradural extramedullary malignant melanoma of the thoracic spine has also been described [149]. Moreover, a remarkable case of extramedullary PSM in a 55-year-old male has been documented; it is thought that there are less than ten cases to this day [150]. In intradural spinal cord melanoma, less than thirty surgical cases have been published [103]. Besides occupying a single structure, it has been reported by Lee CH, et al., Ali Y, et al., and Huang et al. that there are multifocal lesions, particularly in the spine [92,112,150]. According to Somers et al., a diagnosis can be made if no extracranial focus is detected [9]. In the 1980s, Willis et al. stated that to confirm a lesion to be primary in origin, it must meet these three main criteria: I) Absence of cutaneous or eyeball melanoma; therefore, a consultation with an ophthalmologist should be done along with dermatologist input. II) No prior history of surgical resection of skin or eyeball melanoma. III) Viscera is negative for metastatic melanoma [12]. Hayward's criteria are more specific when it comes to identifying primary CNS melanoma, especially since they focus on distinctive CNS features such as leptomeningeal involvement and spinal or intracerebral lesions. In comparison to Willis criteria which focus on the exclusion of the PCM. The combination of both sets of criteria is often the best approach. The distinction between Melanoma of Unknown Primary (MUP) and pCNSM is crucial to avoid misdiagnosis. A reported case described pCNSM metastasizing to the endometrium, but it may represent MUP, as the patient first had brain and nodal metastases [111,151,152].

Clinical manifestation (signs and symptoms): The most common initial complaint among patients with PCNSM is headaches, often accompanied by nausea and vomiting [153]. This constellation of symptoms can be indicative of increased intracranial pressure. Gait disturbances are another common clinical manifestation of PCNSM. These motor symptoms can result from the tumor's location and its impact on neurological function. Intracranial hypertension, characterized by increased pressure within the skull, is frequently observed in patients with PCNSM. It can manifest as painful headaches and is a notable clinical feature.

In some cases, patients may develop hydrocephalus, which can lead to symptoms such as chronic headaches and eyeball pain [111]. Although less frequent, hydrocephalus can occur as a complication of PCNSM. An intriguing clinical case mentioned involves a patient who lost their sense of taste for several months before the initial diagnosis [118]. This unusual symptom highlights the potential variability in clinical presentations of PCNSM.

It is essential to differentiate between metastatic melanoma and PCNSM as their clinical presentations can vary significantly. Metastatic melanomas tend to present with numerous intracranial tumors and systemic metastases and are more common in older individuals. In contrast, PCNSM are typically diagnosed in relatively younger patients (usually under 50 years old) and may

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be associated with pigmented cutaneous nevi [18]. The clinical presentation of PCNSM can vary depending on the state of the disease, whether it is localized or has metastasized to other internal organs. This variation underscores the need for a comprehensive evaluation and diagnostic workup. The historical use of spinal myelograms for detecting tumors like PSM marked an era where localization of tumor sites was possible but provided no insights into their composition. However, the advent of MRI has revolutionized the field, offering a non-invasive and comprehensive approach to visualizing PCNSM. Gomori et al., Damadian et al. and others were the earliest to explain the reason behind the shorting of T1 relaxation time in 1974 and 1986, respectively [154–156]. PCNSM MRI differs depending on the contents of the tumor if it is Melanotic, Amelanotic, and /or hemorrhagic, and whether it is new or old blood collection. This is done by susceptibility-weighted sequences that would reflect the presence of hemosiderin in the mass [27]. PCM could either be Melanotic, Amelanotic, Mixed, or hemorrhagic. Typically, Melanotic melanoma (containing >10% melanotic cells on histopathology) is T1 hyperintense and T2 hypointense caused by the presence of paramagnetic elements in the melanin pigment. Others argue, emphasizing that it is primarily because of hemorrhage (blood products). Amelanotic (melanomas have less than 10% of melanin-containing cells), are either isointense or hypointense on T1W images and isointense to hyperintense on T2W scans. Heterogeneous MRI signals characterize mixed melanoma. Melanoma and hemorrhagic-type lesions account for approximately 70% of malignant intracranial melanomas. In opposition, spinal cord melanomas do not have specific features on radiographic imaging. Some Lipid-like structures could be distinguished from PCM by CT as they could look like PCNSM on MRI. Another beneficial diagnostic tool is 123I-iodoamphetamine in single-photon emission computed tomography (SPECT).

PCNSM can present with radiographic features that resemble other conditions, such as glioblastoma and Arteriovenous malformations (AVMs) [2,157]. This similarity underscores the importance of postoperative immunohistochemistry pathology reports for accurate diagnosis. Glioblastoma is characterized by poorly circumscribed infiltration and significant perilesional edema. In contrast-enhanced MRI, glioblastomas often exhibit heterogeneous enhancement, contrasting with PCNSM.

AVMs typically show low signal intensity on T1-weighted images and high signal intensity with signal voids on T2-weighted images, similar to the appearance of PCNSM on MRI. They are also usually enhanced by contrast. Distinguishing between the two is crucial [128]. Melanotic schwannomas, although rare, are another consideration in the differential diagnosis. They account for less than 1% of all nerve sheath tumors. MRI shows their appearance is distinct from PCNSM, often appearing as T1-weighted isointense or hypointense and T2-weighted isointense or hyperintense. On CT, they appear hyperdense with uniform or peripheral enhancement [158,159].

Differentiating between primary and metastatic melanoma is vital for prognosis estimation. Metastatic melanoma involves multiple organs outside the brain and is often not associated with neurocutaneous syndromes. Survival rates for metastatic melanoma are generally shorter than for PCNSM. Metastatic melanoma lesions are multiple rapidly engaging organs outside the brain with usually absent neurocutaneous syndromes it is essential to comprehend the difference to estimate life expectancy; it was studied that the median survivals for melanoma metastases nowadays in 40% of patients 5 years while primary melanoma patients can survive over 17 years and almost 28 years in post-operative status cases [69,160,161]. Table 3 exhibits the characteristic and radiological hallmarks of the differential diagnosis [162]. Considering risk factors will lead to plausible initial diagnosis in case PCNSM individuals with congenital melanocytic nevi are prone to progress to have malignant melanoma, roughly 25% of them [163–165]. There is a case included in our review of a 41-year-old patient who had Fitzpatrick skin type IV and a congenital nevus of Ota and was diagnosed with a PIMM lesion against the greater wing of the sphenoid bone [166]. The localization of the tumor raises suspicion for other differentials. Understanding risk factors can aid in initial diagnoses. Individuals with congenital melanocytic nevi are at a higher risk of developing malignant melanoma, which can be critical in considering PCNSM as a diagnostic possibility.The location of the tumor can also

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provide important clues for differential diagnosis. For example, tumors in the pineal gland may raise suspicion of pineocytomas or pineoblastomas, emphasizing the need for a thorough evaluation.

Primary and secondary melanoma have distinct molecular profiles. DNA methylation profiling is an innovative technology that can be useful in distinguishing PCNSM from other conditions. Accurate diagnosis is essential for determining appropriate treatment approaches and estimating patient prognosis [167,168].

Due to its rarity and limited treatment options, there is a lack of established guidelines from the National Comprehensive Cancer Network (NCCN) for managing this particular disease. The primary source of treatment insights primarily stems from published case reports. Nevertheless, surgical intervention is the preferred approach for addressing solid lesions. However, there remains a significant debate regarding the potential advantages of employing chemotherapy, radiotherapy, or immunotherapy in an adjuvant capacity after surgery. Postoperative radio chemotherapy is commonly employed; nonetheless, the precise role of adjuvant radiotherapy remains uncertain. Notably, as early as 1977, Arlant et al. utilized radiotherapy in a pioneering manner, marking what is believed to be one of the earliest instances of such treatment. In this particular case, the patients survived for 56 weeks, and the mean survival after surgical dissection of the tumor and radiotherapy was 6 years and 7 months [138,166]. Wadasadawala et al. recommended utilizing a radiation dose of up to 5400 cGy administered in conventional fractions to achieve more sustained disease control, particularly in cases involving residual disease [18]. An illustrative case involves a 73-year-old patient who significantly extended her survival to 56 weeks through radiotherapy alone [69]. Her treatment plan involved receiving 6,000 cGy over 30 fractions using 18MV photons within a 45-day timeframe. Unfortunately, her demise was attributed to a pulmonary embolism. In contrast, another case involving a pineal gland tumor demonstrated a remarkable four-year survival period following partial tumor resection and adjuvant chemotherapy, consisting of dacarbazine administered intravenously at 150 mg/day for five days, vincristine at 1 mg/day for one day, and ACNU at 100 mg/day for one day [11]. Salpietro et al. strongly oppose and discourage the utilization of this approach for treating small residual malignant melanomas, primarily because it is the least toxic option available [82]. The longest survivor was a 47-year-old male who came for a regular MRI and was found to have mixed iso/hyperdense mass in the right cerebellopontine angle on MRI after being 21 years in complete remission. Initially, he underwent adjuvant chemotherapy employing a Dacarbazine-vindesine-cisplatin regimen for advanced malignant melanoma, along with interferon. Unfortunately, he experienced a relapse shortly thereafter. Given the resistance of the mass to both radiotherapy and chemotherapy, the patient opted for an experimental treatment involving a Newcastle disease virus (NDV)-modified tumor vaccine, administered in conjunction with interferon and β-elemene. This treatment plan included an initial six-month course followed by ongoing maintenance therapy, consisting of interferon and β-elemene administered every 3 to 4 months. Conversely, the longest survivor in primary pineal malignant melanoma was a 49-year-old gentleman who experienced a recurrence after 18 years of being free from cancer [167]. The latest cohort study of 10 patients indicated the ideal treatment for solitary-type PIMMs: firstly, ensure that it is a primary tumor by inspecting carefully other possible sites of melanoma to rule out systemic melanoma, fluorodeoxyglucose (FDG)-positron emission tomography (PET) and biopsy and if confirmed proceed with surgical intervention. Depending on the type of resection, treatment follows accordingly. It was stated that CT-assisted intensity-modulated radiation therapy is of more value [168].

To address this challenging condition, the approved treatment strategy involves administering Methotrexate at a dosage of 10 to 15mg either once or twice weekly as intrathecal chemotherapy. This approach entails the direct destruction of tumor cells within the cerebral spinal fluid (CSF). To enhance the efficacy of this treatment, combining it with whole-brain radiotherapy is recommended, as this facilitates cerebrospinal fluid (CFS) flow to the brain, thereby encouraging deeper penetration of chemotherapy into the brain parenchyma.

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Historically, intrathecal chemotherapy was initiated in a case involving intramedullary spinal melanoma in 1889. This decision was based on the detection of abnormal pigmented cells in the CSF through immunohistochemical analysis. Remarkably, a one-year follow-up MRI showed a clear absence of residual disease, recurrences, or metastatic lesions, highlighting the potential effectiveness of this treatment approach [122].

A novel and recently developed therapeutic agent is the BRAF gene inhibitors such as vemurafenib, dabrafenib, and encorafenib. These inhibitors are a well-accepted form of target therapy for managing cutaneous melanoma. Current research efforts are actively investigating the feasibility and effectiveness of combining these inhibitors with MEK inhibitors, especially following surgical procedures. This approach has demonstrated promising results in terms of improving progression-free survival rates, particularly in patients with brain metastases. This is exemplified by a case involving a patient with primary pineal gland malignant melanoma with a BRAF gene mutation (V600E). This patient was received for treatment with B-Raf inhibitors, such as vemurafenib [169]. However, in metastatic melanoma with a BRAF V600 mutation, combination immunotherapy is more effective, particularly for brain metastases, and is the preferred first-line treatment [170].

It is suspected that the life expectancy of primary pineal malignant melanoma without intervention is 0-12 weeks, radiotherapy alone is 16 weeks, subtotal resection and adjuvant radiotherapy to the whole brain is an entire year, and partial resection and adjuvant chemotherapy is 4 years [6,47]. Sometimes, treatment of Combined Nivolumab and Ipilimumab is proposed guided by the results of CheckMate 204, which has demonstrated that 24 patients (26%) had a complete response and 28 (30%) a partial response in the brain, resulting in a rate of intracranial objective response of 55% in nearly half of the participants [171].

Immunotherapy is a novel treatment modulation that is relativity new hence, few cases have been published only five cases of PCNSM treated with immunotherapy and found a median overall survival of 58 months, with outcomes ranging from 5 to 63 months [2]. None of the case collected in this review received immunotherapy.

A limitation of this study is the study relies on previously published literature, which may introduce biases related to case selection, reporting accuracy, and variations in treatment protocols. In addition, certain cases probably identified as pCNSM had an undetected initial lesion in another location, which could result in misclassification and affect the accuracy of the findings. There are only few published cases, and the data on PCNSM is insufficient [172–175]. Hence more attention should be directed towards patients with PCM in order to serve preferable management.

Conclusion

The most common sites in PIMM are lobes, precisely the frontal lobe, and for PSM, the 10th and 11th thoracic vertebrae, often affecting males in their forties. Surgical intervention alone is the primary treatment for localized mass, followed by adjuvant post-operative radiotherapy chiefly in PSM, as it had better outcomes than PIMM. The best treatment modality for PIMM is yet undetermined, although immunotherapy is a juvenile form of treatment for which the data available on long-term efficacy is scarce.

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