Case Report

Primary melanocytic tumors of the central nervous system: Report of two cases and review of literature

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Abstract

Background: Primary melanocytic tumors of the central nervous system (CNS) represent only 1% of all melanomas. We report two rare cases of primary diffuse leptomeningeal melanomatosis (PDLM; case 1) and primary melanoma of the thoraco-lumbar spine (case 2).

Case Description: In case 1, multiple cerebrospinal fluid (CSF) studies and a brain biopsy were non-diagnostic, with a biopsy of the cauda equina eventually demonstrating malignant melanomatosis. Diagnosis of primary spinal cord melanoma was more straightforward in case 2 with imaging and biopsy.

Conclusion: PDLM and primary intramedullary spinal melanoma are rare variants of primary CNS melanoma. This report contrasts the diagnostic challenges between the two entities and alerts the neurosurgeon into considering the diagnosis with appropriate clinical presentation.

Key Words: CNS melanocytic tumors, diffuse leptomeningeal melanomatosis, primary CNS melanoma

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INTRODUCTION

Although metastatic melanoma is the third most common etiology of central nervous system (CNS) metastasis, primary melanocytic tumors of the CNS are rare and account for only 1% of all melanomas.[5] These lesions arise from melanocytes located within the leptomeninges, and can occur as diffuse or solitary, benign or malignant.[14] Studies on primary CNS melanocytic lesions are few and limited to case reports or small case series.[11] In order to illustrate the clinical spectrum of primary melanocytic tumors of the CNS, we present two rare cases: (1) primary diffuse leptomeningeal melanomatosis (PDLM) and (2) primary thoraco-lumbar spinal melanoma. We also review the literature for clinical, radiological, surgical, and histological findings of these lesions.

CASE REPORTS

Case 1: PDLM

Clinical summary
A 51-year-old male presented with progressive headaches, nausea, vomiting, left hip pain, and fatigue for 3 weeks. Neurological examination showed left leaning an talgi c gait and difficulty with tandem and heel-to-toe walking. Brain magnetic resonance

imaging (MRI) showed extensive leptomeningeal enhancement with a small focus of nodular parenchymal enhancement [Figure 1a and b], and non-specific T2 white matter hypointensities [Figure 1c]. Cerebrospinal fluid (CSF) workup was suggestive of aseptic meningoencephalitis (lymphocyte predominance with elevated total protein and IgG). Over the next week, he had decreasing lower extremity strength. A repeat lumbar puncture (LP) revealed opening pressure of 45, with elevated protein level. Brain MRI was unchanged while spine MRI showed diffuse leptomeningeal nodular enhancement of the cervical, thoracic, and cauda equina nerve roots [Figure 1d–f]. The patient was started on empiric treatment for CNS fungal disease, while CSF serology and culture were pending. Multiple therapeutic LPs were performed during the hospital course with similar abnormal CSF profiles (persistently elevated total nucleated cells and protein, low glucose), but were ultimately non-diagnostic. A right temporal brain biopsy was then performed. Surgical pathology was initially concerning for *Nocardia asteroides* that was later determined as a contaminant. The patient's neurological status continued to deteriorate with intermittent leg weakness and episodes concerning clinical seizures.

Owing to diagnostic dilemma and patient's deteriorating condition, a cauda equina biopsy was performed 3 weeks after the brain biopsy. Frozen section of the nerve root demonstrated pigmented cells, and final surgical pathology revealed primary leptomeningeal melanomatosis [Figure 2]. Tumor cells were strongly immunoreactive for HMB-45 and MART-1, with a high Ki-67 proliferation index. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-18 PET CT) demonstrated absence of abnormal FDG activity outside the CNS.

The patient underwent palliative cranio-spinal radiation treatment with adjuvant Temozolomide. These were poorly tolerated and were discontinued after a month. Three months from initial presentation, he died from cardiopulmonary failure.

Case 2: Primary thoraco–lumbar spinal cord melanoma

Clinical summary

A 75-year-old female presented with 3 months of gradually worsening back pain, along with a week-long history of right foot drop, bilateral lower extremity weakness, tripping and falling without bowel or bladder symptoms. Spinal MRI showed an expansile
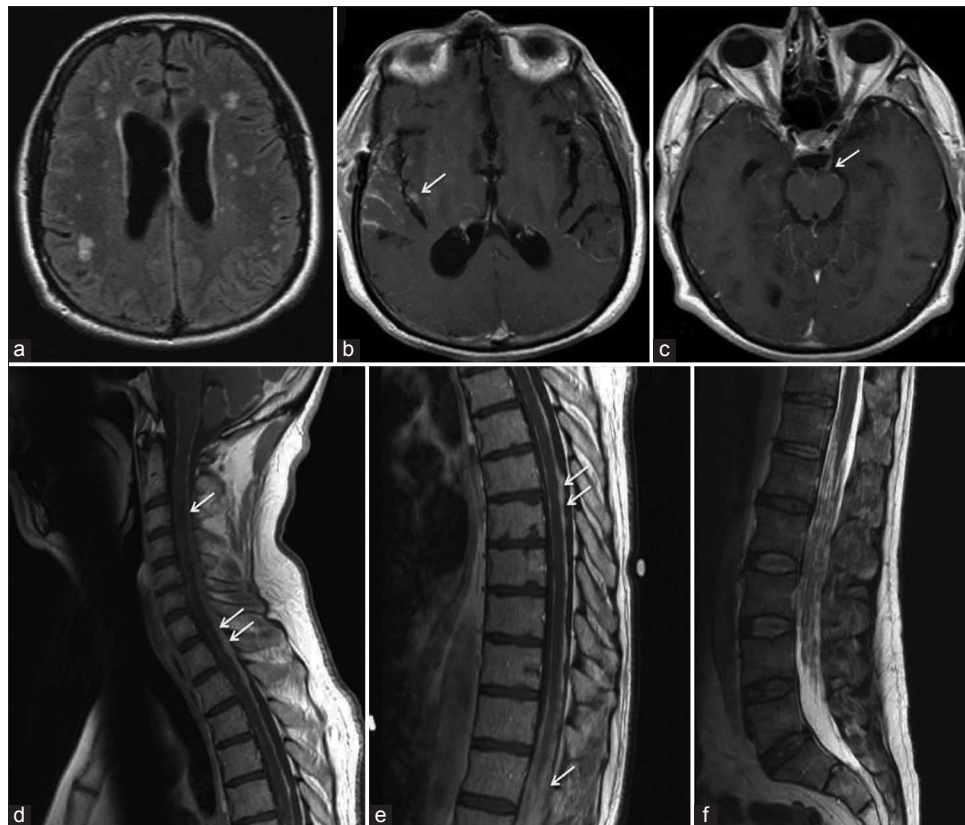

Figure 1: Brain MRI (a–c) showing diffuse areas of FLAIR signal changes (a) and T1W post-gadolinium sequence with diffuse leptomeningeal and nodular parenchymal enhancement (b, arrow) and cranial nerve enhancement (c, arrow showing CNIII). Post-contrast scan of cervical (d) and thoracic (e) spine showing diffuse nodular leptomeningeal enhancement. This was most significant at the lower lumbar region with almost complete obliteration of normal CSF signal on T2WI (f)

intramedullary mass involving the lower thoracic spinal cord and the conus medullaris from T11 to L1, isointense on T1-weighted imaging, and homogenously enhancing following gadolinium injection [Figure 3].

The patient underwent surgical resection of the mass. Pathology revealed a highly cellular tumor with spindle cell morphology and abundant dark pigmentation [Figure 4]. Prominent nucleoli, intranuclear pseudo-inclusions, and mitotic figures were present. Immunohistochemistry staining was positive for melanoma markers S100, MART-1, and HMB-45 and negative for epithelial membrane antigen (EMA) and *BRAF* V600E mutation.

She remained paraparetic postoperatively with no new deficits. Staging workup, including MRI, PET, and ophthalmology evaluation, was negative for evidence of additional disease. She was discharged to a rehabilitation center for physical and occupational therapy. During her last clinic visit, she reported improving sensation in bilateral lower extremities. She is currently undergoing radiotherapy at an outside hospital.

DISCUSSION

Origins

Melanocytes, pigment-producing cells of neural crest origin, migrate during development to the skin, eyes, oro-genital mucosa, and leptomeninges.[8,19] Melanomas predominately develop in the skin, but infrequently primary melanocytic lesions of the CNS may originate from melanocytes in the leptomeninges that undergo transformation.[17,19] The World Health Organization in 2007 sub-classified primary melanocytic lesions into malignant melanoma, melanomatosis, melanocytoma, a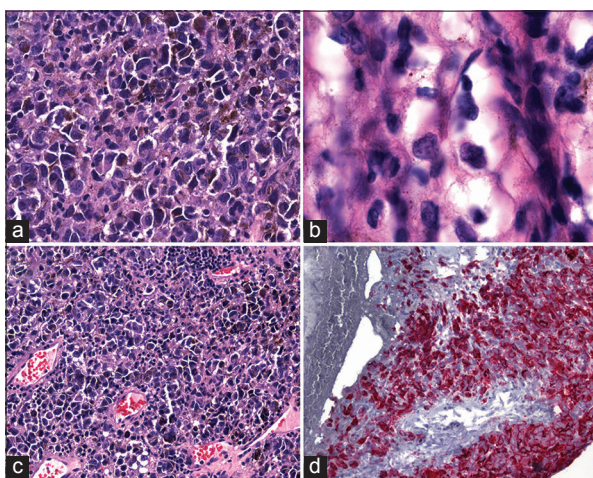nd diffuse melanocytosis.[12,13] These lesions are typically located in the perimedullary and high cervical region, and uncommonly, like in our cases, in the thoraco-lumbar spinal cord and cauda equina.[19]

Clinical presentation

PDLM of the CNS

PDLM (first case) is a rare variant of primary malignant melanoma,[15] occurring more often in adults than in children. To the best of our knowledge, there are only seven cases [Table 1] of this lesion reported in the literature,[1,3,4,6,11,15,20] which is distinguished from diffuse melanosis or melanocytosis by the presence of malignant features. PDLM occurs in patients with age ranging from 20 to 70 years (mean 42 years). PDLM invades brain parenchyma in all cases, with reported involvement of the spinal cord in 43% of cases, of which two cases (67%) have been reported in the cervical thoracic region and one case (33%) in the lower thoracic region with involvement of the cauda equina. The most common presenting symptoms of PDLM include headache (46%), nausea or vomiting (37%), back or neck pain (24%), and weakness (22%).[7] Other clinical features include hydrocephalus, seizure, ataxia, syringomyelia, cranial nerve palsy, intracranial hemorrhage, and neuropsychiatric symptoms.[11] The clinical features of PDLM versus other primary meningeal lesions are presented in Table 2.

Primary melanoma of the CNS

Primary CNS melanomas (second case) occur in patients with age ranging from 20 to 80 years (mean 54 years), with a peak in the fifth decade.[9] In the spinal cord, they most commonly occur in the thoracic region (42%), followed by cervical (35%), thoraco-lumbar (12%), cervicothoracic (8%), and lumbar (4%) regions.[9] Whereas life expectancy is less than 1 year in patients with metastatic melanoma to the CNS, a subgroup of patients with primary CNS melanoma in the literature

Figure 2: Hematoxylin and eosin staining of the cauda equina demonstrating: (a, ×100) pleomorphic spindle cells with prominent nucleoli, mitotic figures (b, ×1250), and melanin pigment. Spreading of neoplastic cells along subpial and perivascular spaces (c, ×100). Immunohistochemical stains for melanoma cocktail including Melan-A demonstrate cytoplasmic reactivity (d)

Figure 3: Midline sagittal magnetic resonance images (MRI) of thoraco-lumbar area. (a) T1-weighted MRI shows the spinal cord tumor at the level of T12, which has high signal intensity relative to that of the cord and combined syrinx. (b) Contrast-enhanced T1-weighted MRI image shows homogenous enhancement

report an average survival of 7 years[9,10] after gross total resection. Therefore, differentiating between primary and metastatic melanoma may be important for prognosis.

Diagnosis

Neuroimaging

Due to the paramagnetic properties of melanin, melanocytic lesions are isointense or hyperintense on
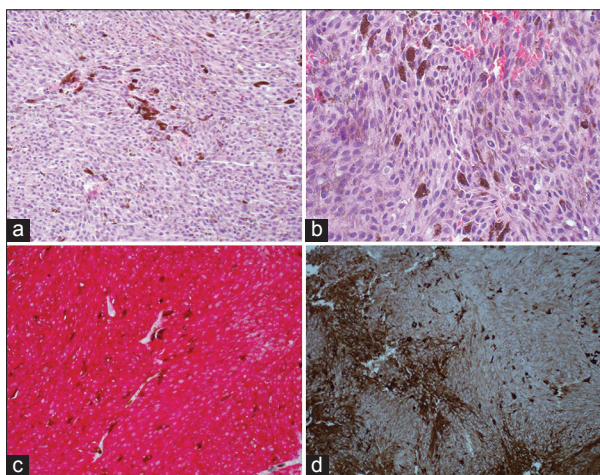

Figure 4: Photomicrograph shows spindle cells with large pleomorphic nuclei (a, H and E, ×20), melanin pigment, and mitoses (b, H and E, ×40). Immunohistochemical stains for melanoma cocktail including Melan-A (c) and S-100 brown chromagen (d) reveal cytoplasmic reactivity (H and E)

T1-weighted imaging, hypointense on T2-weighted imaging,[4,16] and demonstrate intense enhancement with gadolinium.[16] These characteristics vary depending on the melanocytic content and hemorrhage. Because the radiographic features are nonspecific, the differential diagnosis is extensive, including infectious conditions and metastatic carcinoma. Therefore, to establish the diagnosis, imaging must be supplemented with CSF studies and histopathology (when the CSF studies are inconclusive but a melanocytic lesion is strongly suspected).[15] PDLM has a tendency to appear as diffuse meningeal thickening on CT and MRI, whereas primary melanoma appears dense and nodular.[16] No distinguishing imaging characteristics separate primary malignant melanoma from metastatic melanoma; therefore, careful examination for the presence of melanoma elsewhere is necessary to exclude a primary lesion.

Primary diffuse leptomeningeal melanomatosis

Lumbar puncture. The diagnosis of PDLM is notoriously difficult to make.[2,13,15] Clinically, PDLM can mimic a wide variety of other conditions, including lymphoma, metastatic carcinoma, viral encephalitis, and bacterial and fungal meningitis. The diagnosis can be established with identification of melanocytes on cytological examination of CSF.[17] However, the utility of CSF is dependent on the number and degree of pigmentation of cells. Isolated neoplastic cells in the

Table 1: Literature review: PDLM

Study	Pub year	Sex/age	Presenting symptoms	Site	MRI dx	CSF dx	Histo dx	Chemo	Rad	Other interv	Survival
Gaetani et al.	1993	22/F	L iliac pain, bilateral motor weakness	Brain, cervical, thoracic	Yes	No	Yes	No	No	No	>8 months
Celli et al.	2001	53/M	Psychasthenia, amnesia	Brain	Yes	Inconclusive, no malignant cells	Yes	No	No	No	Not reported
Pirini et al.	2003	68/F	Headache, vomiting, mental deterioration	Brain	Yes	No neoplastic cells	Postmortem+ S-100, +vimentin, +HMB-45	No	No	VP shunt	3 years
Demir et al.	2008	32/M	Headache, vomiting, complex partial seizure	Brain, cervical, thoracic spine	Yes	Inconclusive, no malignant cells	Postmortem	No	No	No	1 week
Liubinas et al.	2010	43/M	Progressive headache, drowsiness, confusion	Brain	Yes	↑OP, ↑protein, atypical cells, no malignant cells	Yes+S-100, +vimentin, +tyrosinase	No	No	VP shunt, serial LPs, decadron	"Few days"
Zadro et al.	2010	34/M	Papilledema, flaccid leg, weakness, cognitive impairment	Brain, thoracic spine cauda equina	Yes	↑WBC (lymphocytes), ↑protein, ↓glucose, no malignant cells	Yes+Melanin-A, +HMB-45, +vimentin	No	Yes	No	2 months after radiation
Arias et al.	2011	40/F	Subacute headaches, visual impairement, meningismus	Brain	Yes	↑Protein, no malignant cells	Yes	No	No	No	Not reported
Current study	NA	51/M	Progressive headache, fatigue, imbalance	Brain, cervical, thoracic, lumbar spine	Yes	↑WBC (lymphocytes), ↑protein, ↓glucose, no malignant cells	Yes	Yes, not tolerated	Yes	No	3 months after presentation

Pub: Publication year, dx: Diagnosis, histo: Histology, chemo: Chemotherapy, rad: Radiation, interv: Other intervention, sv: Survival, L: Left, R: Right, OP: Opening pressure, F: Female, M: Male

Table 2: Distinguishing clinical features between malignant melanoma, melanomatosis, melanocytoma, diffuse melanocytosis

	Primary CNS melanoma	PDLM	Melanocytoma	Diffuse melanocytosis
Age	15-71 years, peak 5th decade	20-70 years	9-73 years old, peak 5th decade	<10 years or 10-30 years
Incidence	0.005 cases per 100,000	Very rare, unknown	1 per 10 million	Unknown
Sex	1:1 male: Female	1:1 male: Female	Female predominance	Male predominance
No. lesions	Solitary but may metastasize	Extensive	Solitary or multiple	Extensive
Area of occurrence	Predilection for posterior fossa and spinal cord: Thoracic, cervical, thoracolumbar	Parenchymal, thoracic, less commonly cervical and cauda equina	Cervical, thoracic spine usually intradural, extramedullary	Supra-and infra-tentorial leptomeninges, cerebellum, pons, medulla, temporal lobes
Brain involvement	Brain and/or spine	Always	No	No
Extra-neural disease	May metastasis. Association with neurocutaneous melanosis	No	Melanotic lesions to kidneys, adrenal glands	Association with neurocutaneous syndromes, neurofibromatosis-1, Sturge-Weber syndrome, Dandy Walker syndrome
Clinical symptoms	Intracranial hypertension, hydrocephalus, focal deficits from compression, SAH, seizure	Headache, weakness, cognitive impairement	Intracranial hypertension or hemorrhage, neuropsychiatric, spinal cord compression, seizures	Intracranial hypertension, hydrocephalus, seizure, ataxia, syringomyelia, cranial nerve palsy
Clinical course	Aggressive	Aggressive	May be aggressive, 71% recurrence within 5 years	Aggressive
Treatment	Total resection, postoperative radiotherapy	No definitive treatment. VP shunt is palliative	Total resection, adjuvant radiotherapy. Preliminary results positive with intrathecal chemotherapy	No definitive treatment. Tumor debulking and VP shunt insertion palliative. Role of chemo and radiation unclear
Prognosis	Better with total resection versus partial resection. Average survival after surgery and radiotherapy 6 years and 7 months	Poor	Recurrence common at 5 years	Poor

PDLM: Primary diffuse leptomeningeal melanomatosis, CNS: Central nervous system, VP: Ventriculoperitoneal, SAH: Subarachnoid hemorrhage

CSF may not be present in a sample or can escape recognition.[15] In our case, despite multiple (six) LPs sent for cytology, neither malignant cells nor melanin-containing cells were identified. Nonspecific but abnormal CSF findings concerning chronic aseptic meningitis (elevated opening pressure, high protein, low glucose) further delayed diagnosis. In a review of PDLM cases reported in the literature [Table 1], diagnosis could only be established after biopsy or postmortem (in two cases), with CSF studies being non-diagnostic. Histopathological diagnosis was obtained from cerebral biopsy in four cases, from spinal biopsy in one case, and from cerebral autopsy in two cases. Our case is unique among other PDLM cases in that initial brain biopsy was negative, requiring biopsy of cauda equina for the final diagnosis. This case highlights the variability of neoplastic cells in CSF and tissue, and the difficulty in reaching this diagnosis, requiring repeat biopsy.

Surgical appearance and histopathology
Biopsy is often the only definitive diagnostic procedure in cases of suspected PDLM in which CSF analysis and neuroimaging are inconclusive, such as in case 1. Biopsy is performed much less frequently than LP or neuroimaging

due to associated risks, and may not be considered indicated in cases where CSF cytology is negative.[13] We believe that repeat LP and/or biopsy may be indicated for cases where CSF studies are persistently abnormal in the absence of malignant cells, whose presence may be variable.

Dense sheets of pleomorphic, spindle-shaped cells with melanin are typical histological findings.[16] In contrast to melanocytoma, PDLM diffusely infiltrates the leptomeninges, and unlike diffuse melanosis, demonstrates features of malignancy.[15] PDLM, similar to other primary melanocytic lesions, is usually immunoreactive for anti-melanoma antibody (HMB-45), anti-melanosomal antibody MART-1 (Melan-A), and tyrosinase,[11] and is variably reactive with vimentin and S-100 protein.[11] Unlike melanin containing meningioma, melanocytic lesions do not demonstrate immunoreactivity for EMA.[18] Some of the distinguishing features of the different types of melanocytic lesions involving the CNS are detailed in Table 2.

Primary CNS melanoma
Surgical appearance and histopathology
Intraoperatively, primary malignant melanoma may appear as a solid, darkly pigmented tumor with varying

amounts of hemorrhage.[16] Immunohistochemistry findings are similar to other melanocytic lesions.[11] The diagnosis of primary CNS melanoma relies on imaging and biopsy, and less on CSF studies, in which extensive dissemination in CSF may not have occurred. The dense appearance of melanoma may provide a more accessible target for successful biopsy than a diffuse process such as PDLM or diffuse melanocytosis.

CONCLUSION

To conclude, PDLM and primary CNS melanoma are rare tumors that present a diagnostic and therapeutic challenge to the neurosurgeon and oncologist. We emphasize the difficulty of establishing a diagnosis of PDLM through CSF cytology and imaging alone. The presence of neoplastic cells may be highly variable in CSF and in tissue samples. Because of the diffuse appearance of PDLM versus the more dense appearance of primary CNS melanoma, in some cases, repeat biopsy may be needed to establish the diagnosis. Our understanding of these tumors relies on a small number of reported cases; thus diagnosis and management are not standardized. Diagnosis of this condition requires a high index of suspicion and familiarity with the clinical, CSF, and radiographic findings. This condition can mimic other causes of chronic aseptic meningitis, and biopsy may be the only definitive diagnosis when radiographic and CSF findings are inconclusive.

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