

# Pearls & Oy-sters: Primary Diffuse Leptomeningeal Melanocytosis

## A Diagnostic Conundrum

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## Abstract

Primary diffuse leptomeningeal melanocytosis (PDLM) is an extremely rare CNS tumor with nonspecific clinicoradiologic features that overlap considerably with aseptic meningitis posing significant diagnostic and therapeutic challenges. We present one such case report of a patient treated empirically at first presentation as aseptic viral meningitis based on MRI and CSF analysis. Diagnosis of PDLM was established subsequently through meningeal biopsy that demonstrated a melanocytic tumor with fine granular melanin pigment without significant mitoses. Her systemic and ocular examination was unremarkable. Whole-body 18F-fluorodeoxyglucose PET/CT (FDG-PET/CT) did not identify any other primary site. Following ventriculoperitoneal shunt to relieve hydrocephalus, she was treated with definitive craniospinal irradiation plus whole-brain boost and remains stable on periodic clinicoradiologic surveillance. Optimal management of PDLM lacks consensus with role of radiotherapy, chemotherapy, targeted therapy and immunotherapy being controversial.

## Pearls

- Primary diffuse leptomeningeal melanocytosis (PDLM) is an extremely rare CNS tumor that mimics aseptic meningitis clinicoradiologically posing considerable diagnostic and therapeutic challenges.
- Meningeal hyperintensities on precontrast T1-weighted MRI can guide radiologists to raise differential diagnosis of melanocytic tumors.
- Diagnosis of PDLM is established through neurosurgical biopsy of a CNS lesion with negative findings outside the neuraxis.

## Oy-sters

- Leptomeningeal metastases are far more common than PDLM mandating detailed dermatologic and ocular examination to rule out malignant melanoma arising outside the CNS.
- Whole-body imaging using 18F-fluorodeoxyglucose PET/CT (FDG-PET/CT) is recommended to distinguish primary from metastatic melanocytic tumors in the CNS.

## Case Description

A 20-year-old female student, born of nonconsanguineous marriage with no significant birth history and normal developmental milestones, presented with insidious onset of intermittent dull-aching holocranial headaches that were not associated with any aura, photophobia, or precipitating/aggravating factors. Her physical examination was unremarkable with no evidence of fever, lymphadenopathy, or focal neurologic deficits, except for a single pigmented hairy lesion (3 × 2 cm) over the skin of the anterior abdominal wall since birth with no recent

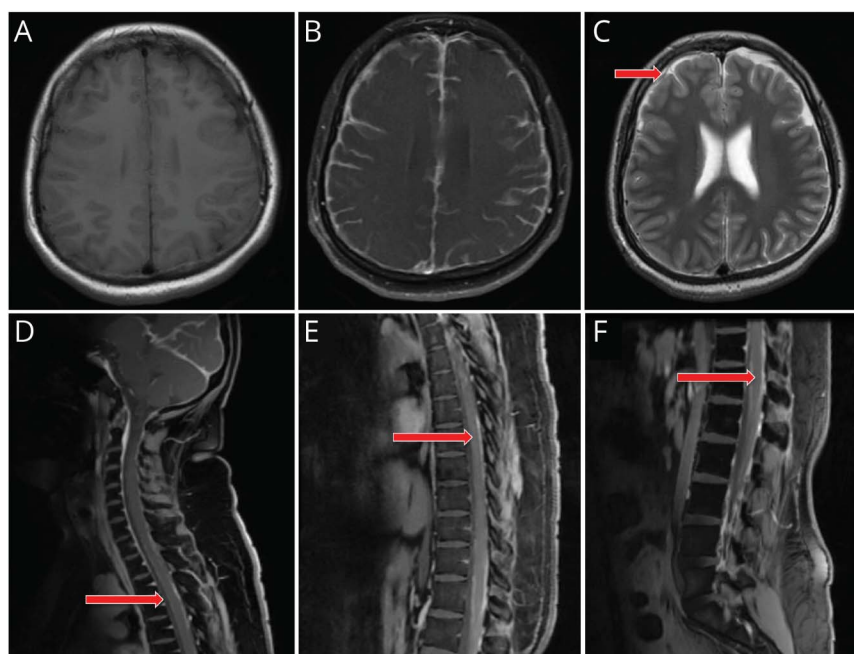
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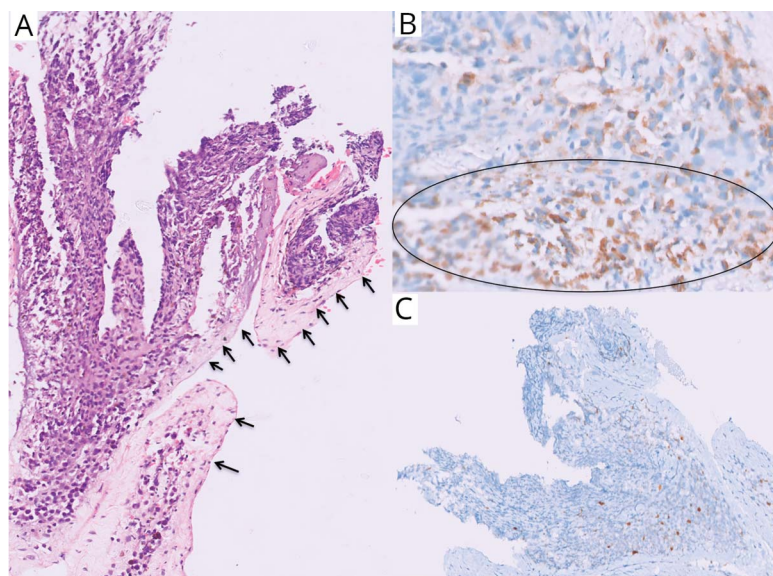
change in size, color, or texture (eFigure 1, [links.lww.com/WNL/C676](https://links.lww.com/WNL/C676)). MRI showed diffuse involvement of the intracranial leptomeninges including basal cisterns, isointense on T1-weighted images, hypointense on T2-weighted images with intense postcontrast images (Figure 1) suspicious for tubercular meningitis. Lumbar puncture revealed increased opening CSF pressure with high cellularity (40 cells/mm<sup>3</sup> predominantly lymphocytes). Normal CSF biochemistry (glucose 56 mg/dL; protein 55 mg/dL) including low (9U/L) adenosine deaminase levels coupled with lack of fever and meningismus virtually ruled out pyogenic or tubercular meningitis. However, given high prevalence of tuberculosis in the patient's geographic region, tubercular meningitis still needed to be ruled out. Further CSF studies including Gram stain, India ink preparation, Ziehl-Neelsen stain for acid-fast bacilli, GeneXpert for *Mycobacterium tuberculosis*, fungal and bacterial cultures were negative. An extended panel for parasitic, viral, and autoimmune diseases was also negative and did not resolve the diagnostic conundrum. A clinicoradiologic diagnosis of aseptic viral meningitis was suspected for which she was started on acyclovir empirically (400 mg 5 times daily for 5 days) under cover of steroids (dexamethasone starting at 8 mg twice daily, tapered every 2 days and stopped in 6 days). However, worsening of headaches prompted repeat MRI that showed persistence of diffuse leptomeningeal enhancement in the brain with new-onset hydrocephalus (eFigure 2, [links.lww.com/WNL/C677](https://links.lww.com/WNL/C677)); sagittal postcontrast screening MRI of the spine showed linear enhancement at the dorsolumbar level (Figure 1). At this time, fundoscopic examination revealed early papilledema.

The patient underwent a ventriculoperitoneal (VP) shunt to relieve hydrocephalus with repeat CSF analysis showing normal biochemistry and negative testing for tuberculosis, rickettsia, scrub typhus, and leptospira. CSF cytospin smears were moderately cellular and showed scattered cells of intermediate size with moderate cytoplasm, round nucleus with opened chromatin, and large prominent nucleoli suggesting atypical cell morphology. Subsequently, she underwent a right temporoparietal craniotomy with dural/arachnoid biopsy for establishing definitive diagnosis. Histomorphology from meningeal biopsy showed fibrocollagenous tissue representing dural collagen with small fragments of a melanocytic tumor composed of bland melanocytes having round to oval nucleus, prominent eosinophilic nucleolus, and scant cytoplasm with fine granular brown intracellular and extracellular melanin pigment deposition with no significant mitotic activity (Figure 2). On immunohistochemistry (IHC), neoplastic cells were immunonegative for cytokeratin, CD3, and CD20 but diffusely positive for HMB-45 and S-100 (Figure 2) with low proliferative activity (MIB-1 labeling index of 1%–2%) leading to the diagnosis of primary diffuse leptomeningeal melanocytosis (PDLM). Additional IHC for BRAFV600E mutation was immunonegative; however, tissue from the small meningeal biopsy was deemed inadequate for further molecular testing. At this time, she also underwent biopsy from the congenital skin lesion, which was confirmed to be a benign intradermal nevus (eFigure 1, [links.lww.com/WNL/C676](https://links.lww.com/WNL/C676)). Her systemic and ocular examination was unremarkable, and whole-body 18F-fluorodeoxyglucose emission tomography/CT (FDG-PET/CT) did not identify any site of primary tumor in the body supporting the diagnosis of PDLM in the CNS.

**Figure 1** Neuraxial Imaging of Primary Diffuse Leptomeningeal Melanocytosis



MRI at index presentation shows diffuse involvement of the intracranial leptomeninges isointense on axial precontrast T1-weighted MRI (A) with intense postcontrast enhancement (B) and corresponding hypointense signals (marked with arrow) on T2-weighted sequence (C). Repeat MRI including postcontrast T1-weighted sagittal screening of the spine showing linear enhancement of spinal leptomeninges with nodularity (marked with arrows) at the lower cervical (D), midthoracic (E), and upper lumbar (F) levels suggestive of diffuse leptomeningeal involvement of entire neuraxis.



Microphotographs of meningeal biopsy showing sheets of bland plump oval-shaped cells (melanocytes) resting on a thin fibrous band of tissue (marked with arrows), with some cells showing cytoplasmic fine brown-colored pigment (A) without significant mitoses (hematoxylin and eosin stain  $\times 200$ ). On immunohistochemistry ( $\times 200$ ), the neoplastic cells are diffusely positive for HMB-45 (B) confirming melanocytic origin (circled area). Occasional cells (2%–3%) show MIB-1 labeling ( $\times 100$ ) suggestive of low proliferative potential (C) of the tumor.

The case was discussed in the institutional neuro-oncology multidisciplinary tumor board following which she was treated with craniospinal irradiation (35 Gy/21 fractions) plus whole-brain boost (14.4 Gy/8 fractions) for neuraxial control. Her posttreatment response assessment MRI (at 3 months) showed stable leptomeningeal enhancement, and she remains clinicoradiologically controlled 1 year from initial diagnosis on periodic surveillance. Ethical approval for this case report was not applicable; the patient provided written consent for publication without identifying information.

## Discussion

Primary melanocytic neoplasms of the CNS represent a spectrum of rare tumors that are derived from melanocytes originating in the neural crest.<sup>1–3</sup> Melanoblasts, precursors of melanocytes, migrate during early embryonic development via the dorsolateral route mainly to the skin and to a lesser extent to mucosa of the aerodigestive and urogenital tract, uvea, and leptomeninges.<sup>2,3</sup> Melanocytic tumors can present as circumscribed tumors arising focally within the CNS or diffuse lesions expanding and spreading along the leptomeninges and Virchow-Robin spaces with variable clinical behavior. The World Health Organization 2021 classification<sup>4</sup> describes melanocytic tumors of the CNS as either circumscribed or diffuse. Circumscribed lesions include melanocytoma (benign/low grade) and melanoma (malignant), whereas diffuse lesions comprise melanocytosis and melanomatosis. Melanocytosis refers to diffuse proliferation of histologically benign-appearing leptomeningeal melanocytes without frank invasion of underlying neuroparenchyma, whereas melanomatosis refers to the aggressive spread of histologically atypical or malignant melanocytes through the leptomeninges often with parenchymal

invasion. The estimated annual incidence of primary leptomeningeal melanocytic neoplasms is approximately 1 in 10 million.<sup>5</sup>

Differentiating PDLM from metastatic melanoma and other pigmented primary tumors of the CNS has remained difficult and challenging for radiologists and pathologists.<sup>6–8</sup> Diffuse melanocytic involvement of the CNS has association with neurocutaneous melanosis<sup>9,10</sup>—a rare, sporadic phakomatoses syndrome characterized by the association of congenital melanocytic nevi with overlying hypertrichosis. One particularly notable nevus associated with leptomeningeal involvement is the nevus of Ota,<sup>11</sup> which occurs on the face and eyelid unilaterally and frequently involves the sclera and choroid of the eye. Leptomeningeal melanosis is a benign primary melanocytic condition of the CNS that causes hyperpigmentation of the pia and arachnoid mater, which remains largely asymptomatic, is detected incidentally on neuroimaging, and frequently occurs in association with dermatologic conditions such as giant congenital melanocytic nevi as part of neurocutaneous melanosis.<sup>9–11</sup> Screening MRI in children with congenital melanocytic nevi detects leptomeningeal melanosis in nearly 6%–20% of patients. On follow-up, the overwhelming majority of such children with leptomeningeal melanosis remain asymptomatic; however, 2%–3% develop neurologic signs and symptoms with evidence of neoplastic and malignant transformation.<sup>10</sup>

PDLM can have a wide spectrum of initial presentation with nonspecific symptoms like headache, nausea, vomiting, and seizures generally due to obstructive hydrocephalus but may also present with altered mental status and focal neurologic deficits.<sup>3,12</sup> The paramagnetic properties of melanin render these tumors hyperintense on T1-weighted and hypointense

on T2-weighted MRI<sup>6-8</sup> with intense postcontrast enhancement that provides clues for imaging-based diagnosis. In addition to T1 shortening, melanin presents low signal on gradient echo T2\*-weighted sequence and susceptibility-weighted imaging providing additional diagnostic clues.<sup>6</sup> Important differential diagnoses include aseptic meningitis, tubercular meningitis, subarachnoid hemorrhage, neurosarcoidosis, and neoplastic meningitis from metastatic melanoma. Detailed dermatologic and ocular examination and whole-body FDG-PET/CT are generally recommended to exclude leptomeningeal metastases from a malignant melanoma arising outside the CNS.<sup>12</sup> The molecular genetics of primary melanocytic neoplasms of the CNS has been relatively unexplored. Novel insights in molecular alterations<sup>2,3</sup> underlying primary melanocytic tumors of the CNS have reported activating mutations of genes encoding G proteins (*GNAQ* and *GNA11*) in adults along with *BAP1* inactivation and *SF3B1*, *EIF1AX*, and *NRAS* mutations in children (particularly in the context of neurocutaneous melanosis). Oncogenic mutations in the *BRAF* (50%), *N/K/H-RAS* (25%), and *NF1* (15%) genes that account for the majority of cutaneous melanomas are rarely described in CNS melanocytic tumors.<sup>2,3</sup> MEK inhibition has recently been demonstrated to reduce disease burden and improve symptom control in children with *NRAS*-driven primary CNS melanomas<sup>13</sup> and could benefit PDLM patients with *NRAS* mutations. Tumor mutational burden of primary CNS melanocytic neoplasms is not well described compared with other melanomas, which typically demonstrate high mutational burden and are amenable to immunotherapeutic blockade with checkpoint inhibitors in the advanced/metastatic setting. There are extremely sparse data on the safety and efficacy of immunotherapy in PDLM limited to few case reports<sup>3,14</sup> with favorable responses and promising short-term outcomes.

Optimal management of PDLM lacks consensus and remains controversial. Its nonspecific clinicoradiologic characteristics and rarity pose diagnostic and therapeutic challenges with management recommendations being based on personal and/or institutional biases and preferences. Focal melanocytic tumors such as primary melanocytoma and melanoma are typically treated with surgery followed by adjuvant RT. However, surgical extirpation is not feasible in diffuse melanocytic tumors due to widespread infiltration of the neuraxis. CSF diversion via VP shunt to relieve hydrocephalus and anticonvulsant medication for seizure prophylaxis have been the mainstay of symptomatic/supportive care. The largest literature review<sup>15</sup> involving 33 proven cases of PDLM reported dismal prognosis with progressive neurologic deterioration resulting in death few months after diagnosis. The role of definitive RT (including CSI) and/or systemic therapy either chemotherapy, targeted therapy or immunotherapy remains to be clearly defined.<sup>12,14,15</sup>

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<b>Tejpal Gupta, MD</b>	Department of Radiation Oncology, Tata Memorial Hospital (TMH)/Advanced Centre for Treatment Research & Education in Cancer (ACTREC), Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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