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Pearls & Oy-sters: Primary Diffuse Leptomeningeal Melanocytosis: A Diagnostic Conundrum

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Primary diffuse leptomeningeal melanocytosis (PDLM) is an extremely rare central nervous system tumor with non-specific clinico-radiological 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 magnetic resonance imaging and cerebrospinal fluid (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-fluoro-deoxy-glucose positron emission tomography/computed tomography (FDG-PET/CT) did not identify any other primary site. Following ventriculo-peritoneal shunt to relieve hydrocephalus, she was treated with definitive craniospinal irradiation plus whole-brain boost and remains stable on periodic clinico-radiological surveillance. Optimal management of PDLM lacks consensus with role of radiotherapy, chemotherapy, targeted therapy and immunotherapy being controversial.

Keywords: CNS; diffuse; melanocytosis; meningitis; MRI; therapy

Pearls:

Primary diffuse leptomeningeal melanocytosis (PDLM) is an extremely rare central nervous system (CNS) tumor that mimics aspetic meningitis clinico-radiologically posing considerable diagnostic and therapeutic challenges.

Meningeal hyperintensities on pre-contrast T1-weighted magnetic resonance imaging (MRI) can guide radiologists to raise differential diagnosis of melanocytic tumors.

Diagnosis of PDLM is established through neuro-surgical biopsy of a CNS lesion with negative findings outside the neuraxis.

Oy-sters:

Leptomeningeal metastases are far more common than PDLM mandating detailed dermatological and ocular examination to rule out malignant melanoma arising outside the CNS.

Whole-body imaging using 18F-fluoro-deoxy-glucose positron emission tomography/computed tomography (FDG-PET/CT) is recommended to distinguish primary from metastatic melanocytic tumors in the CNS.

Case description:

A twenty-year-old female student, borne of non-consanguineous 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 neurological deficits, excepting for a single pigmented hairy lesion (3 x 2cm) over the skin of the anterior abdominal wall since birth with no recent change in size, color, or texture (eFigure 1). Magnetic resonance imaging (MRI) showed diffuse involvement of the intracranial leptomeninges including basal cisterns, isointense on T1-weighted images, hypointense on T2-weighted images with intense post-contrast images (Figure 1) suspicious for tubercular meningitis. Lumbar puncture revealed increased opening cerebrospinal fluid (CSF) pressure with high cellularity (40 cells/mm^3 predominantly lymphocytes). Normal CSF biochemistry (glucose-56mg/dl; protein-55mg/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-Nelson stain for acid fast bacilli, GeneXpert for Mycobacterium tuberculosis, fungal and bacterial cultures were negative. An extended panel for parasitic, viral, and auto-immune

diseases was also negative and did not resolve the diagnostic conundrum. A clinico-radiological diagnosis of aseptic viral meningitis was suspected for which she was started on acyclovir empirically (400mg five times daily for 5 days) under cover of steroids (dexamethasone starting at 8mg 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); sagittal post-contrast screening MRI of the spine showed linear enhancement at the dorso-lumbar level (Figure 1). At this time, fundoscopic examination revealed early papilloedema.

The patient underwent a ventriculo-peritoneal (VP) shunt to relieve hydrocephalus with repeat CSF analysis showing normal biochemistry and negative 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 temporo-parietal craniotomy with dural/arachnoid biopsy for establishing definitive diagnosis. Histomorphology from meningeal biopsy showed fibro-collagenous 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 immuno-negative for cytokeratin, CD3, and CD20 but diffusely positive for HMB-45 and S-100 (Figure 2) with low proliferative activity (MIB-1 labelling index of 1-2%) leading to the diagnosis

of primary diffuse leptomeningeal melanocytosis (PDLM). Additional IHC for BRAFV600E mutation was immuno-negative; 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). Her systemic and ocular examination was unremarkable and whole-body 18F-fluoro-deoxy-glucose emission tomography/computed tomography (FDG-PET/CT) did not identify any site of primary tumor in the body supporting the diagnosis of PDLM in the central nervous system (CNS).

The case was discussed in the institutional neuro-oncology multi-disciplinary tumor board following which she was treated with craniospinal irradiation (35Gy/21 fractions) plus whole-brain boost (14.4Gy/8 fractions) for neuraxial control. Her post-treatment response assessment MRI (at 3-months) showed stable leptomeningeal enhancement and she remains clinico-radiologically controlled 1-year from initial diagnosis on periodic surveillance. Ethical approval for this case report was not applicable; however, 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.[1-3] 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.[2,3] 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[4] describes melanocytic tumors of the CNS as either 'circumscribed' or 'diffuse'. Circumscribed lesions include melanocytoma (benign/low-grade) and melanoma (malignant), while diffuse lesions comprise of 'melanocytosis' and 'melanomatosis'. Melanocytosis refers to diffuse proliferation of histologically benign appearing leptomeningeal melanocytes without frank invasion of underlying neuro-parenchyma, while 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 population.[5]

Differentiating PDLM from metastatic melanoma and other pigmented primary tumors of the CNS has remained difficult and challenging for radiologists and pathologists.[6-8] Diffuse melanocytic involvement of the CNS has association with neurocutaneous melanosis[9,10] - a rare, sporadic phakomatoses syndrome characterised by the association of congenital melanocytic nevi with overlying hypertrichosis. One particularly notable nevus associated with leptomeningeal involvement is the nevus of Ota,[11] which occurs on the face and eyelid unilaterally and frequency 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 neuro-imaging, and frequently occurs in association with dermatologic conditions such as giant congenital melanocytic nevi as part of neurocutaneous melanosis.[9-11] Screening MRI in children with congenital

melanocytic nevi detects leptomeningeal melanosis in nearly 6-20% of patients. On follow-up, overwhelming majority of such children with leptomeningeal melanosis remain asymptomatic; however, 2-3% develop neurological signs and symptoms with evidence of neoplastic and malignant transformation.[10]

PDLM can have a wide spectrum of initial presentation with non-specific symptoms like headache, nausea, vomiting, and seizures generally due to obstructive hydrocephalus, but may also present with altered mental status and focal neurological deficits.[3,12] The paramagnetic properties of melanin renders these tumors hyperintense on T1-weighted and hypointense on T2-weighted MRI[6-8] with intense post-contrast 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.[6] Important differential diagnoses include aseptic meningitis, tubercular meningitis, subarachnoid hemorrhage, neuro-sarcoidosis, and neoplastic meningitis from metastatic melanoma. Detailed dermatological and ocular examination as well as whole-body FDG-PET/CT is generally recommended to exclude leptomeningeal metastases from a malignant melanoma arising outside the CNS.[12] The molecular genetics of primary melanocytic neoplasms of the CNS has been relatively unexplored. Novel insights in molecular alterations[2,3] underlying primary melanocytic tumors of the CNS have reported activating mutations of genes encoding G proteins (*GNAQ, GNA11*) in adults along with *BAP1* inactivation, *SF3B1, EIF1AX* and *NRAS* mutations in children (particularly in the context of neurocutaneous melanosis). Oncogenic mutations in *BRAF* (50%), *N/K/H-RAS* (25%), and *NF1* (15%) genes that account for majority of cutaneous melanomas are rarely

described in CNS melanocytic tumors.[2,3] MEK inhibition has recently been demonstrated to reduce disease burden and improve symptom control in children with *NRAS*-driven primary CNS melanomas[13] and could benefit PDLM patients with *NRAS* mutations. Tumor mutational burden of primary CNS melanocytic neoplasms is not well described compared to other melanomas which typically demonstrate high mutational burden and are amenable to immunotherapeutic blockade with checkpoint inhibitors in the advanced/metastatic setting. There is extremely sparse data on the safety and efficacy of immunotherapy in PDLM limited to few case reports[3,14] with favorable responses and promising short-term outcomes.

Optimal management of PDLM lacks consensus and remains controversial. Its non-specific clinico-radiological characteristics and rarity poses 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 anti-convulsant medication for seizure prophylaxis have been the mainstay of symptomatic/supportive care. The largest literature review[15] 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.[12,14,15]

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References:

1. Liubinas SV, Maartens N, Drummond KJ. Primary melanocytic neoplasms of the central nervous system. J Clin Neurosci. 2010;17(10):1227-1232.
2. Küsters-Vandevelde HV, Küsters B, van Engen-van Grunsven AC, et al. Primary melanocytic tumors of the central nervous system: a review with focus on molecular aspects. Brain Pathol. 2015;25(2):209-226.
3. Baumgartner A, Stepien N, Mayr L, et al. Novel Insights into Diagnosis, Biology and Treatment of Primary Diffuse Leptomeningeal Melanomatosis. J Pers Med. 2021;11(4):292.
4. Louis DN, Perry A, Wesseling P, Brat DJ, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro-oncol. 2021;23(8): 1231-1251.
5. Yao-Yu H, Hun-Tai Y, Wei-Hua Li, et al. Primary Leptomeningeal Melanoma Mimicking Meningitis: A Case Report and Literature Review. J Clin Oncol. 2015;32(12):e57-61.
6. Pirini MG, Mascalchi M, Salvi F, et al. Primary diffuse meningeal melanomatosis: radiologic-pathologic correlation. AJNR Am J Neuroradiol 2003;24:115-118.
7. Smith AB, Rushing EJ, Smirniotopoulus JG. Pigmented lesions of the central nervous system: radiologic-pathologic correlation. Radiology 2009;29(5):1503-1524.
8. Hossain FA, Marquez HJ, Veltkamp DL, et al. CT and MRI findings in leptomeningeal melanocytosis. Radiol Case Rep. 2020;15(3):186-189.

9. Qian M, Ren H, Qu T, et al. Spectrum of clinical, neuroimaging, and cerebrospinal fluid features of adult neurocutaneous melanocytosis. Eur Neurol. 2018;80:1-6.
10. Ruggieri M, Polizzi A, Catanzaro S, et al. Neurocutaneous melanocytosis (melanosis). Childs Nerv Syst 2020;36(10):2572-2596.
11. Balmaceda, C. M, Fetell MR, Powers J, et al. Nevus of Ota and leptomeningeal melanocytic lesions. Neurology. 1993;43(2):381-386.
12. Saadeh YS, Hollon TC, Fisher-Hubbard A, et al. Primary diffuse leptomeningeal melanomatosis: description and recommendations. J Clin Neurosci. 2018;50:139-143.
13. Kinsler VA, O'Hare P, Jacques T, Hargave D, Slater O. MEK inhibition appears to improve symptom control in primary *NRAS*-driven CNS melanoma in children. Br J Cancer. 2017;116:990-993.
14. Palacka P, Slopovsky J, Makovnik M, et al. A case report of a patient with inoperable primary diffuse leptomeningeal melanomatosis treated with whole-brain radiotherapy and pembrolizumab. Medicine (Baltimore). 2022;101:3.
15. Eichberg DG, Achua JK, Locatelli E, et al. Primary diffuse leptomeningeal melanomatosis: case report and literature review. World Neurosurg. 2019;122:648-655.

Figure 1: Neuraxial imaging of primary diffuse leptomeningeal melanocytosis

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

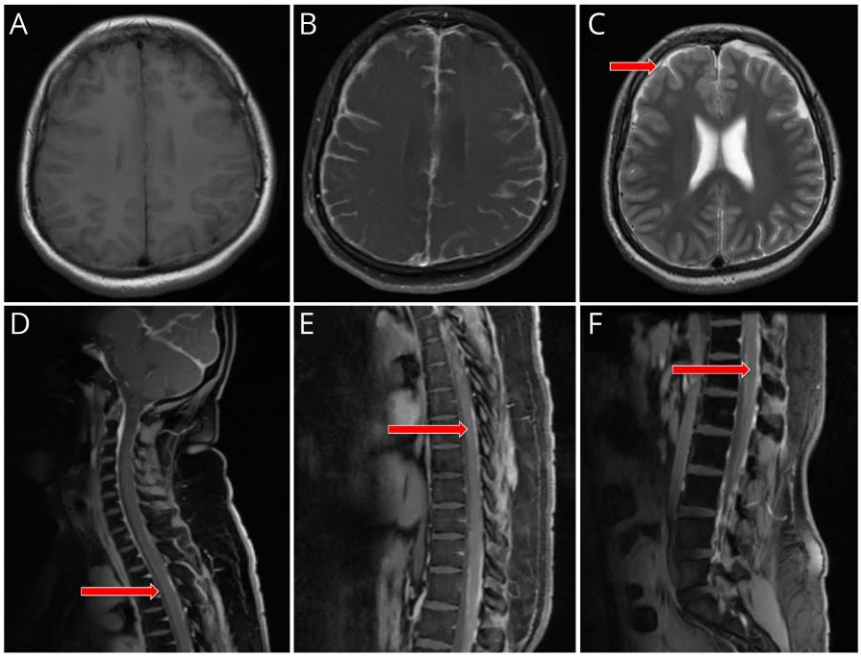
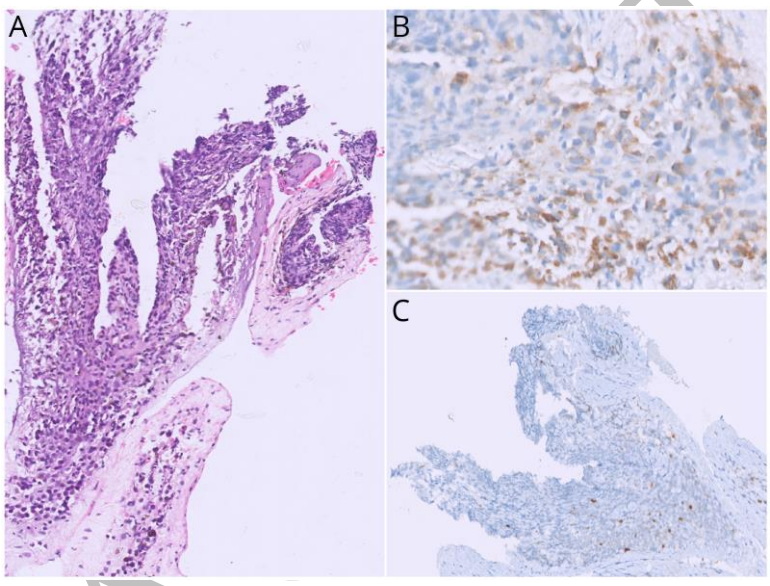


Figure 2: Histopathological features of primary diffuse leptomeningeal melanocytosis

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 & eosin stain x 200). On immunohistochemistry (x 200), the neoplastic cells are diffusely positive for HMB-45 (B) confirming melanocytic origin (encircled area). Occasional cells (2-3%) show MIB-1 labelling (x 100) suggestive of low proliferative potential (C) of the tumor



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