Neurology Asia 2025; 30(4) : 1271 – 1274

The skin knew first: A diagnostic chase for primary diffuse leptomeningeal melanocytosis

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Abstract

Primary diffuse leptomeningeal melanocytosis (PDLM) is a rare and clinically aggressive primary tumor of the central nervous system that arises from leptomeningeal melanocytes. We report the case of a 38-year-old male presenting with subacute-onset headache, nausea, and vomiting, without focal neurological deficits. Magnetic Resonance Imaging (MRI) of the brain revealed diffuse leptomeningeal enhancement with cystic changes and mild ventriculomegaly. Despite an extensive infectious and inflammatory workup, no etiology was identified. Surgical biopsy during temporal craniotomy revealed a melanocytic neoplasm with atypical pigmented cells invading the cortex. Immunohistochemistry was positive for S100 and HMB-45, with a Ki-67 index of 7–8%, confirming the diagnosis of primary diffuse leptomeningeal melanocytosis. Whole-body 18F-fluorodeoxyglucose emission tomography (FDG-PET/CT) excluded systemic melanoma, establishing the primary CNS origin. The patient underwent whole-brain radiotherapy and temozolomide-based chemotherapy but succumbed during treatment. This case underscores the diagnostic challenges of primary diffuse leptomeningeal melanocytosis, which mimics more common infectious or inflammatory meningitides. A high index of suspicion, especially in the presence of congenital melanocytic nevi and characteristic radiological findings, should prompt early tissue diagnosis. Given its rapid progression and dismal prognosis, prompt recognition is crucial for initiating timely intervention.

Keywords: Primary diffuse leptomeningeal melanocytosis; CNS melanoma; leptomeningeal enhancement; melanocytic neoplasm; intracranial melanoma; HMB-45; Ki-67.

INTRODUCTION

Primary diffuse leptomeningeal melanocytosis (PDLM) is a rare and aggressive variant of primary central nervous system (CNS) tumors.[1] Taking its origin from the melanocytes of the neural crest cells, it is found to be present in approximately 1 in 10-20 million people.[2] The rarity of this condition is underscored by the infrequency of case reports in the literature and presents a considerable diagnostic challenge due to its highly variable clinical behavior. With a wide spectrum of initial presentation, PDLM can manifest with non-specific symptoms ranging from headache, nausea, and vomiting, to seizures, altered mental status, and focal neurological deficits.[3,4] Due to its diagnostic complexity and aggressive clinical course, PDLM is associated with a poor prognosis, highlighting the need for prompt and thorough investigation should a clinical suspicion arise.[4-6]

CASE REPORT

A 38-year-old man with no significant past medical history was referred from a primary health care center, with an insidious onset of intermittent, moderate to severe, dull-aching, frontal and bitemporal headaches for fifteen days. It was associated with multiple episodes of nausea and vomiting, with no precipitating, aggravating, or relieving factors, and was not associated with aura or photophobia. There was no associated history of fever, and his neurological examination was within normal limits, with no signs of raised intracranial pressure. His physical examination was unremarkable, except for multiple hairy hyperpigmented lesions on the back (15 x 10 cm), the extensor surface of the right forearm (3 x 1 cm), and the anterior chest (1 x 1 cm). (Figure 1) These were present since birth and were not associated with recent changes in size, color, texture, or boundaries.

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Date of Submission: 7 August 2025; Date of Acceptance: 12 September 2025

https://doi.org/10.54029/2025vdd

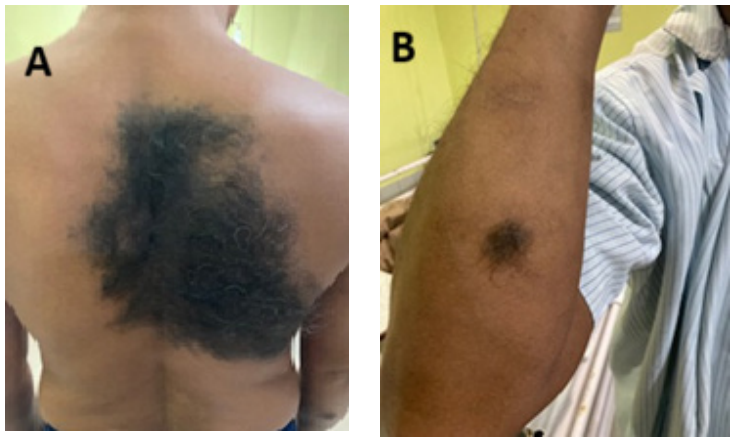

Figure 1. (A) Showing hairy hyperpigmented lesions (15 x 10 cm) on the back and (B) showing lesion in extensor surface of the right forearm (3 x 1 cm).

His post-contrast Magnetic Resonance Imaging (MRI) of the brain revealed diffusely thick leptomeningeal enhancement along bilateral cerebral sulcal spaces, and cerebellar folia, with adjacent dural enhancement (Figure 2 – green arrows). One cystic locule at the left anterior temporal convexity showed internal T1 hyperintensity (Figure 2 - red arrow). Mild dilatation of the bilateral lateral ventricles was also present on imaging.

Laboratory investigations, including complete blood count, metabolic panel, and autoimmune panel, were within normal limits. Serum Angiotensin-converting enzyme (ACE), IgG4, and ANCA were normal, ruling out granulomatous disease. Chest X-ray and abdominal ultrasound were unremarkable. Lumbar puncture showed raised opening pressure with hemorrhagic and lymphocytic pleocytosis. CSF biochemistry and adenosine deaminase were normal. Infectious

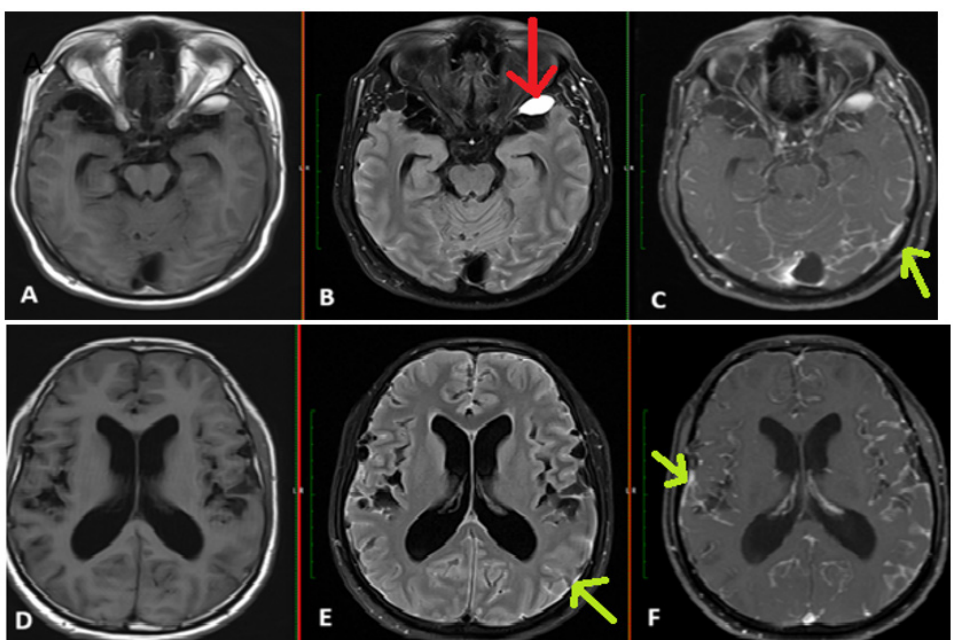

Figure 2. MRI Brain (T1W, T2 FLAIR, and post contrast) showing one cystic locule at the left anterior temporal convexity with internal T1 hyperintensity. [(B), red arrows] Diffuse thick leptomeningeal enhancement is seen along bilateral cerebral sulcal spaces and cerebellar folia, with adjacent dural enhancement. [(C), (D), and (E), green arrows].

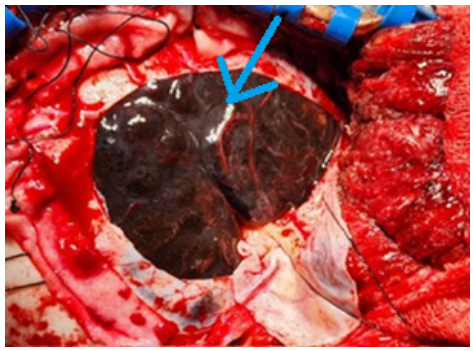

Figure 3. Showing greyish-black hyperpigmented discoloration of the meninges. (blue arrow)

workup was negative, ruling out meningitis.

The patient subsequently underwent elective left temporal craniotomy with biopsy of the dura, arachnoid, and temporal lesion. Intraoperatively, greyish-black hyperpigmented meninges were observed (Figure 3: blue arrow)

Histopathology revealed a melanocytic neoplasm composed of atypical melanocytes in sheets and nests, with eosinophilic cytoplasm, round to ovoid nuclei, prominent nucleoli, nuclear hyperchromasia, pleomorphism, and scattered mitoses. Many cells contained intracytoplasmic melanin. Focal cortical invasion was noted. Immunohistochemistry showed diffuse positivity for S100 and HMB-45, with a Ki-67 labeling index of 7–8%.

Whole-body 18F-fluorodeoxyglucose emission tomography/CT (FDG-PET/CT) did not reveal any other primary tumor in the body, and a diagnosis of PDLM was made. The patient was offered whole brain radiotherapy to a dose of 20 Gy in five fractions over 6 days, following which the patient was referred to a medical oncologist and was started on temozolomide during his chemotherapy. The patient passed away during treatment.

DISCUSSION

In the CNS, melanocytes normally exist in the leptomeninges located on the inferior surface of the cerebrum and the anterolateral surface of the brainstem and the spinal cord. Melanocytosis of the CNS involves diffuse leptomeninges and generally occurs in association with rare dermatological phakomatoses. It is a rare neurocutaneous melanosis, characterized by giant congenital melanocytic nevi with overlying hypertrichosis.[7] Leptomeningeal melanomatosis, primary or secondary, should be kept in the differential diagnosis, especially in the presence of such skin lesions, as screening MRI in children with congenital nevi shows an incidence of melanosis in 6-20% of patients.[8]

The diagnostic dilemma in this case arose due to the initial common presentation of sub-acute onset headache and vomiting in a young person. This presentation can have many differential diagnoses, including meningitis, migraine, CNS tumor, or cerebrovascular accident.

Melanotic melanoma typically appears hyperintense on T1-weighted and hypointense on T2-weighted MRI due to melanin's paramagnetic effect from stable free radicals.[9] In this case, diffuse leptomeningeal T1 hyperintensity was observed, raising suspicion for primary CNS melanoma. A whole-body PET-CT scan revealed no extracranial lesions, including in the congenital hairy nevus, supporting a primary central origin.[9]

Histologically, primary CNS melanomas show pleomorphic, pigmented tumor cells with frequent mitoses, necrosis, hemorrhage, and parenchymal invasion. In contrast, leptomeningeal melanosis lacks atypia and brain invasion. Most tumors are HMB-45-positive (86–97%) and express S-100, though the latter is less specific.[10]

PDLM remains a highly aggressive, radioresistant tumor with a poor prognosis; a

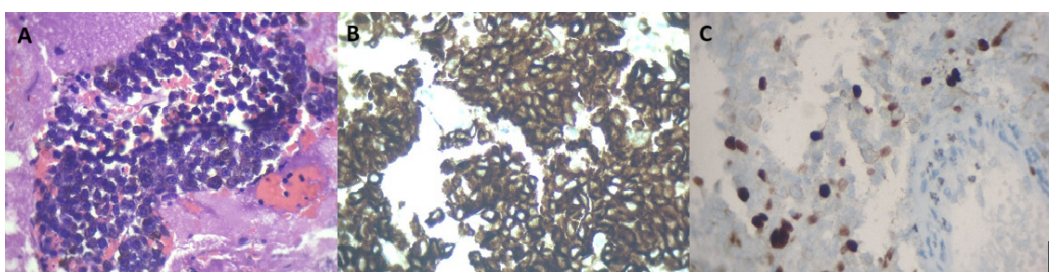

Figure 4: (**A**) The photomicrographs show a cellular neoplasm comprising sheets of polygonal cells with eosinophilic cytoplasm and vesicular nuclei with large, prominent nucleoli. Many of the tumor cells contained intracytoplasmic melanin (H & E, X400) (**B**) Tumor cells were diffusely positive for HMB-45 (Immunoperoxidase, X400), with (**C**) a Ki-67 labelling index of 7-8% (Immunoperoxidase, X400).

high index of suspicion, especially in the presence of congenital melanocytic nevi and characteristic radiological findings, should prompt early tissue diagnosis, which is critical for initiating timely intervention.[11]

DISCLOSURE

Ethics: Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Financial support: None

Conflict of interest: None

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