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Diagnostic difficulties of primary diffuse leptomeningeal melanocytosis of the central nervous system: clinical case

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ABSTRACT

Primary diffuse leptomeningeal melanocytosis (PDLM) is a rare neoplastic lesion of the central nervous system, characterized by diffuse infiltration of the leptomeninges by melanocytes without apparent invasion into the brain parenchyma. Diagnosing the disease is challenging due to its nonspecific clinical presentation and the lack of clear neuroimaging criteria, necessitating morphological and immunohistochemical studies for definitive verification.

This article presents a clinical case of a patient with progressive neurological impairments, diagnostic challenges, and postmortem verification of PDLM. The key differential diagnostic aspects, the morphological structure of the tumor, and its immunohistochemical profile are described. Additionally, neuroimaging data are provided, demonstrating characteristic changes associated with PDLM. The presented clinical case highlights the necessity of a multidisciplinary approach to managing patients with chronic meningeal lesions of unknown etiology and underscores the importance of further research in molecular diagnostics and potential treatment strategies.

Keywords: primary diffuse meningeal melanocytosis, neuroimaging, immunohistochemistry, pathology

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Диагностические сложности первичного диффузного меланоцитоза ЦНС: клиническое наблюдение

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РЕЗЮМЕ

Первичный диффузный лептоменингеальный меланоцитоз (ПДЛМ) – редкое опухолевое поражение центральной нервной системы, характеризующееся диффузной инфильтрацией мягких мозговых оболочек мела*н*оцитарными клетками без явной инвазии в паренхиму головного мозга. Диагностика заболевания представляет сложность в связи с неспецифичностью клинической картины и отсутствием четких нейровизуализационных критериев, что требует проведения морфологического и иммуногистохимического исследований для окончательной верификации диагноза.

В статье представлен клинический случай пациента с прогрессирующими неврологическими нарушениями, диагностическими сложностями и постмортальной верификацией ПДЛМ. Описаны ключевые дифференциально-диагностические аспекты, особенности морфологического строения опухоли и ее иммуногистохимический профиль. Также представлены данные нейровизуализационных исследований, демонстрирующие характерные изменения, сопровождающие ПДЛМ. Описанный случай демонстрирует необходимость междисциплинарного подхода при ведении пациентов с хроническими менингеальными поражениями неустановленной этиологии и подчеркивает значимость дальнейших исследований в области молекулярной диагностики и потенциальных терапевтических стратегий.

Ключевые слова: первичный диффузный менингеальный меланоцитоз, нейровизуализация, иммуногистохимия, патоморфология

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Primary leptomeningeal melanocytic neoplasms (PLMN) represent a heterogeneous group of extremely rare tumors of the central nervous system (CNS), possessing unique histological and molecular characteristics that fundamentally distinguish them from other melanocytic or pigmented lesions, including cerebral and leptomeningeal melanoma metastases. Incidence rates for this group of neoplasms in the general population have not yet been established due to the lack of representative cohort studies, and clinical and biological data on the pathogenesis and natural course of the disease remain highly limited [1].

PLMN of the CNS originate from melanocytes, which are derived from the neural crest and migrate into the leptomeningeal membranes during embryogenesis [2]. According to the current WHO classification of CNS tumors (WHO 2021), this group manifests either as a solitary, well-demarcated, and voluminous leptomeningeal mass or as a diffuse / multifocal leptomeningeal dissemination.

The WHO currently differentiates four categories of primary melanocytic tumors of the CNS: meningeal melanocytosis and melanomatosis, melanocytoma (benign / low-grade malignancy), and meningeal melanoma (malignant), each characterized by specific features of the clinical course, malignant potential, and corresponding prognostic indicators [3].

Primary diffuse leptomeningeal melanocytosis (PDLM) is characterized by diffuse proliferation of histologically benign leptomeningeal melanocytes without apparent invasion into the brain parenchyma, whereas primary diffuse melanomatosis appears as an aggressive dissemination of histologically atypical or malignant melanocytes through the leptomeningeal membranes with invasion into the brain tissue [3]. Epidemiological data indicate that the incidence of

meningeal melanocytomas is 1 case per 10,000,000 population per year, while the annual incidence of meningeal melanomas is only 0.005 case per 100,000 population [4].

A major diagnostic challenge for clinicians and pathologists in these lesions is the differential diagnosis of PLMN from metastatic melanoma and other pigmented primary CNS tumors. This aspect has critical clinical significance for determining prognosis and selecting an appropriate treatment strategy [5, 6]. The diagnostic algorithm is further complicated by the fact that PDLM may present with a wide range of nonspecific symptoms, including cephalic disorder, nausea, vomiting, and seizures (primarily due to the development of obstructive hydrocephalus), changes in mental status, and focal neurological symptoms, often leading to diagnosis by exclusion [7, 8].

PDLM like other primary CNS tumors exhibits characteristic neuroimaging patterns. On computed tomography (CT) scans, melanocytic tumors appear as hyperdense lesions with typical contrast enhancement. Magnetic resonance imaging (MRI) provides more detailed visualization, demonstrating hyperintensity of tumors on T1-weighted images and iso- or hypointensity on T2-weighted images. However, MRI findings can only suggest a melanocytic nature of the tumor but cannot differentiate a primary tumor from a secondary one [9, 10].

Despite the existing arsenal of diagnostic methods, morphological examination of tumor tissue using immunohistochemical techniques remains the gold standard for verifying primary melanocytic tumors of the CNS [11]. Timely and accurate diagnosis of PDLM is crucial for determining the treatment strategy and assessing the prognosis, given the malignant potential of benign lesions and the overall trend toward poor outcomes in diffuse disease. However, the lack of a standardized treatment approach makes patient management extremely challenging [12, 13]. The study of clinical cases, such as the one presented in this article, contributes to a better understanding of disease progression, diagnosis, and potential treatment strategies.

CLINICAL CASE

Patient N., 48 years old, was admitted to the inpatient emergency unit with a moderate condition and a polymorphic clinical presentation, including progressive lower extremity weakness, generalized asthenia, visual disturbances, cephalic disorder predominantly localized in the frontal region, and cervicalgia.

Medical History. The onset of the disease was noted in early January 2024, when the aforementioned symptoms first appeared. The patient initiated the diagnostic process independently and underwent MRI of the brain and cervical spine, which revealed signs of moderately pronounced internal compensatory hydrocephalus and degenerative dystrophic changes in the cervical spine (C6/C7 disc protrusion, uncovertebral and facet joint arthrosis, spondylosis, and vertebral artery asymmetry).

After an unsuccessful attempt at self-medication using nonspecific therapeutic agents, the patient was initially hospitalized in the neurology department. Following the inpatient examination and treatment, a diagnosis of “Migraine without aura with autonomic symptoms and rare moderate-intensity episodes” was established. However, the prescribed therapy upon discharge was ineffective, and no positive clinical dynamics were observed.

Subsequently, the clinical symptoms progressed, with the onset of diplopia, nausea, systemic dizziness, and intensifying lower-limb paraparesis, leading to significant limitations in motor activity. Notably, no hyperthermic syndrome was detected. The patient was admitted to the infectious diseases department with a fully developed clinical presentation, and after excluding an infectious etiology, he was transferred to a specialized neurology unit for further therapeutic decision-making and plasmapheresis.

At the initial neurological examination, a combination of neurological abnormalities was identified, including flaccid lower-limb paraparesis, sensory disturbances, peripheral facial nerve paresis, and signs of bulbar syndrome. Based on the medical history and neurological status, a preliminary diagnosis was established: “Acute inflammatory demyelinating polyneuropathy with flaccid tetraparesis (mild in the upper limbs, pronounced in the lower limbs), mild left-sided facial nerve palsy, early manifestations of bulbar syndrome without respiratory impairments”.

During hospital stay in the neurology department, the patient underwent repeat MRI of the brain, which revealed the following pathological changes: symmetrical triventricular open / normal-pressure hydrocephalus, involvement of the corpus callosum, symmetrical involvement of the tectospinal tracts (suggestive of a degenerative process or sequelae of toxic damage), and changes in the leptomeningeal membranes of the basal brain regions, characteristic of leptomeningitis (Fig. 1–3).

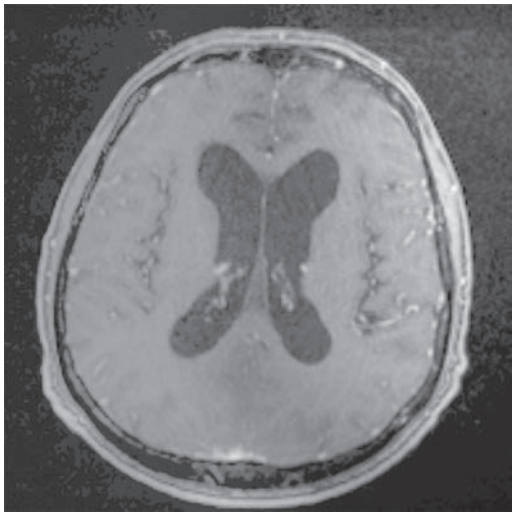


Fig. 1. Multislice Computed Tomography of the Brain.

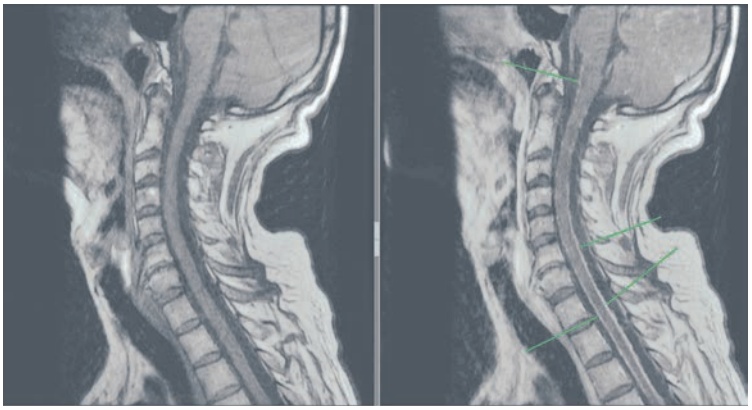


Fig. 2. Multislice Computed Tomography of the Brain.

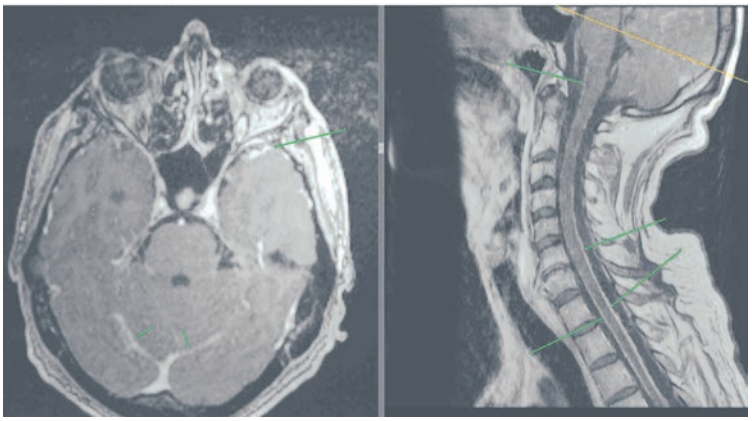


Fig. 3. Multislice Computed Tomography of the Brain. Axial T1-weighted image of the brain and sagittal T1-weighted image of the cervical spine were performed after the administration of the contrast agent. Multiple areas of enhanced MR signal from the pia mater of the brain and spinal cord.

Axial T1-weighted image of the brain after the administration of a contrast agent. Small areas of enhanced MR signal from the pia mater, more pronounced in the occipital region, narrowing of cerebrospinal fluid space at high convexity, expansion of the lateral ventricles in the context of hydrocephalus.

Despite comprehensive conservative therapy, the patient's condition was characterized by a steadily declining trajectory, and at day 18 of hospital stay, amidst progressing neurological deficits, a fatal outcome occurred.

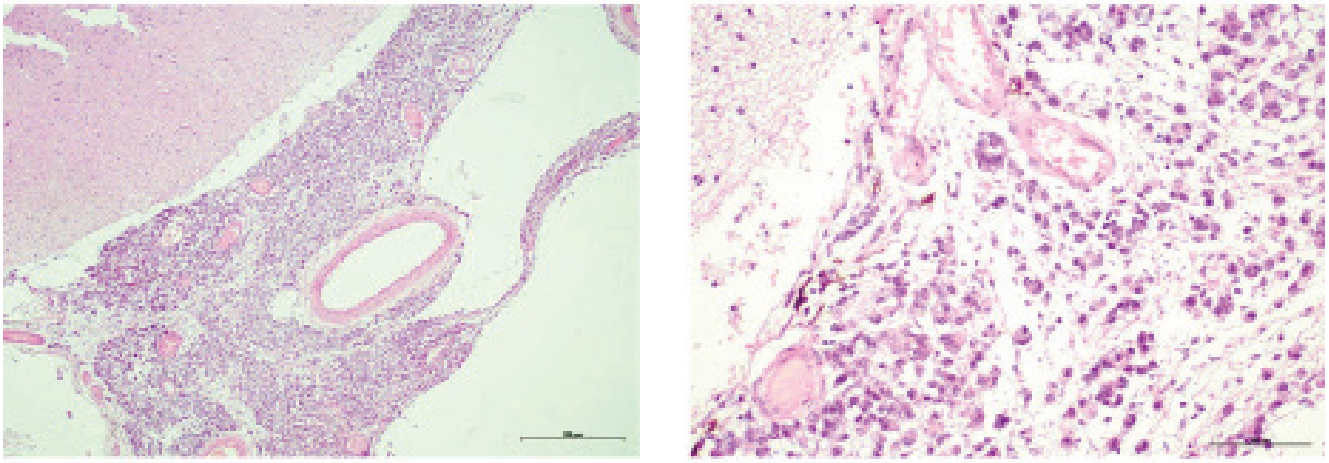
The final clinical diagnosis was formulated as follows: "Chronic leptopachymeningitis of unspecified etiology, progressive course with cranial nerve involvement (bilateral involvement of the optic, oculomotor, and abducent nerves, left-sided facial nerve involvement); bulbar dysfunction;

flaccid tetraparesis predominantly affecting the lower extremities".

Sagittal T1-weighted images of the cervical and upper thoracic spine before and after the administration of the contrast agent. Areas of enhanced MR signal from the unevenly thickened pia mater of the spinal cord are more pronounced at the upper thoracic spine.

PATHOLOGIC EXAMINATION

At autopsy, an area of discoloration of the meninges to a brownish, translucent, dull shade was observed bilaterally at the lateral sulcus of the brain, extending to the transverse temporal gyri between the frontal and parietal lobes. Similar changes were identified in the pia mater at the transition zone between the medulla oblongata and the spinal cord, as well as in the cerebellar region. Fragments of the meninges from these areas were collected for a subsequent microscopic examination. The microscopic analysis revealed that the pia mater was totally affected by a diffusely growing tumor composed of large and medium-sized epithelioid polygonal, round, and oval cells. Tumor cells exhibited eosinophilic cytoplasm, relatively monomorphic nuclei with coarse chromatin, and distinctly visible small, round, eosinophilic nucleoli. A distinguishing feature was the presence of brown pigment granules within the cytoplasm of most tumor cells. The tumor displayed areas of microalveolar architecture. The mitotic activity of the tumor was low, with 1–2 mitoses per 10 high-power fields at ×40/0.65 magnification. There were no necrotic tissue changes, and no evidence of tumor cell invasion into the neuroparenchyma was detected (Fig. 4).



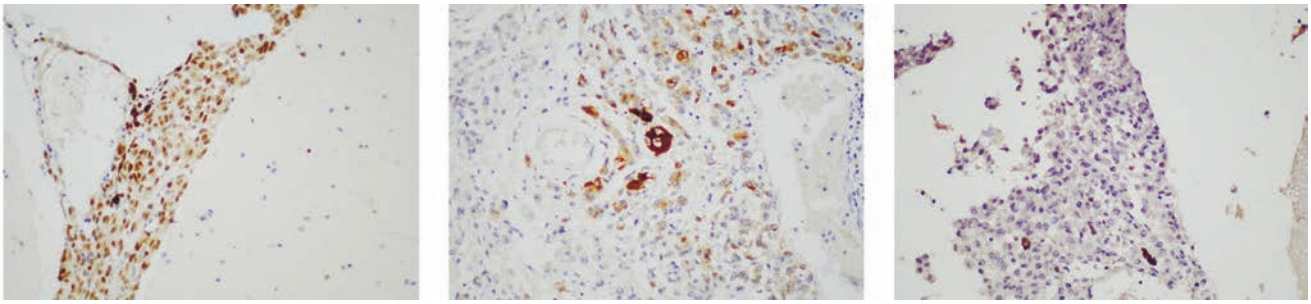
a *b*

Fig. 4. Primary Diffuse Meningeal Melanocytosis of the Pia Mater (Microphoto). The pia mater is diffusely infiltrated by small-cell tumor with brown pigment granules in some cells. Hematoxylin and eosin stain: *a* – ×4/0.10; b – ×10/0.25.

IMMUNOHISTOCHEMISTRY AND MOLECULAR GENETIC STUDY

To verify the histogenesis of the meningeal neoplasm, an immunohistochemical study was performed using the Leica Bond – Max fully automated staining system (Germany). Tumor cells exhibited positive expression of melanocytic markers: SOX10 (clone EP268, Cell Marque) and Melan-A (clone A103, Dako). The Ki-67 proliferative activity index (clone SP6, Cell Marque) was 2% in most parts of the tumor (Fig. 5). Additionally, a molecular genetic study was conducted to detect mutations in the *BRAF* gene, which are characteristic of certain melanocytic neoplasms.

The results indicated the absence of activating *BRAF* mutations, which is relevant for differential diagnosis and understanding the molecular pathogenesis of this tumor. Given the absence of extracranial melanocytic tumors in the patient that could be considered as a primary lesion, the diffuse involvement of the pia mater without invasion of tumor cells into the brain parenchyma, and the results of immunohistochemistry and molecular genetic studies, the histological type of the tumor was verified as primary diffuse leptomeningeal melanocytosis.



a *b* *c*

Fig. 5. Immunohistochemistry of the Pia Mater Tissue Samples with a Tumor. Immunohistochemistry: *a* – positive nuclear expression of SOX10 in tumor cells, ×4 / 0.10; *b* – positive cytoplasmic expression of Melan-A in tumor cells, ×10 / 0.25; *c* – positive nuclear expression of Ki67 in single cells, ×10 / 0.25.

FINAL PATHOLOGIC DIAGNOSIS

Primary Disease. Primary diffuse meningeal melanocytosis with involvement of the pia mater of both cerebral hemispheres, medulla oblongata, pons, cerebellum, and cervical segment of the spinal cord, as well as cranial nerve involvement (bilateral involvement of the optic, oculomotor, and abducent nerves, left-sided facial nerve involvement); bulbar dysfunction; flaccid tetraparesis (based on medical history data).

Complications. Triventricular symmetrical open normal-pressure hydrocephalus (MRI findings). Hospital-acquired total polysegmental bilateral fibrinous purulent pneumonia with abscess formation. Sepsis. Acute cardiovascular failure. Acute respiratory failure. Brain edema.

Comorbidities. Atherosclerosis of the aorta, type II–IV atherosclerotic plaques with a distribution of up to 30%.

DISCUSSION

PDLM is a rare CNS pathology characterized by diffuse infiltration of the leptomeninges by melanocytes without apparent invasion into the brain parenchyma. The described fatal clinical case demonstrates significant diagnostic challenges, highlighting the importance and necessity of a multidisciplinary approach to managing patients with progressive neurological symptoms of unclear etiology. The clinical manifestation of PDLM is nonspecific, including cephalic disorder, progressive muscle weakness, visual disturbances, cognitive impairments, and seizures.

In the presented case, there was gradual progression of neurological symptoms mimicking various neurological diseases, particularly demyelinating polyneuropathy, which explains the substantial delay in establishing the final diagnosis. Contrast-enhanced MRI allowed for visualization of pathological changes characteristic of leptomeningeal involvement. However, a definitive diagnosis was only made post-mortem following the pathologic examination. This underscores the limited capacity of modern neuroimaging methods in the differential diagnosis of primary melanocytic neoplasms of the CNS, which is consistent with literature data [14, 15].

The autopsy confirmed diffuse infiltration of the leptomeninges by pigmented cells with low proliferative activity. The application of immunohistochemical markers SOX10 and Melan-A allowed for reliable identification of the melanocytic nature of tumor cells, while the low Ki-67 proliferation index (< 2%) indicated a formally benign biological potential of the tumor.

During the differential diagnosis, metastatic melanoma, leptomeningeal carcinomatosis, and melanotic astrocytoma were considered. The absence of primary extracranial melanocytic lesion, the lack of invasive growth into the brain parenchyma, and low mitotic activity allowed to exclude malignant neoplasms from the differential diagnosis list. The prognostic evaluation of PDLM remains uncertain due to the rarity of the condition and the lack of sufficient data on its natural course. In this case, despite the absence of classical histological signs of malignancy, an aggressive clinical course was observed. The most likely determining factors in the progression of the disease were diffuse infiltration of the leptomeninges and the subsequent development of secondary hydrocephalus.

Treatment strategies for PDLM are limited due to the lack of pathogenetically grounded treatment

methods. The literature describes cases of surgical intervention in localized forms of the disease and potential use of chemotherapy and radiation therapy in cases of malignant transformation; however, the effectiveness of these therapeutic modalities in diffuse PDLM remains debatable and requires further study.

CONCLUSION

The presented clinical case underscores the necessity of including primary diffuse meningeal melanocytosis in the differential diagnosis algorithm for patients with chronic meningeal lesions of unknown etiology. Modern neuroimaging methods provide diagnostic value, yet they lack sufficient specificity to establish a definitive diagnosis, which must rely on comprehensive morphological and immunohistochemical studies.

Promising research areas include investigation of the molecular genetic characteristics of PDLM, which could potentially contribute to the development of innovative diagnostic approaches and targeted treatment strategies. Accumulating and systematizing data on this rare pathology within multicenter studies may help optimize diagnostic algorithms and therapeutic approaches, thereby improving patient prognosis in PDLM.

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