ABSTRACT

Background: The diffuse meningeal melanomatosis (MM) is part of a group of rare melanocytic diseases. Aiming to emphasize aspects of the natural history, diagnosis and treatment of this rare disease we decide to report the present case. Cade Description: A 17 years-old girl presenting with headache for the last 45 days, followed by episodes of agitation and hallucinations. CT scan revealed mild meningeal enhancement on the right hemisphere. MRI revealed significant diffuse dura-mater thickening, invading cerebral cortex and white matter, including the brain stem. The study of cerebrospinal fluid showed the presence of neoplastic cells, cytology confirmed melanocytes. The histological study, carried out from the brain biopsy, showed diffuse melanocytes infiltrating the meninges, at the subarachnoid space and cerebral cortex. The histological diagnosis was diffuse MM. Conclusions: In conclusion, diffuse MM is a rare condition of malignant characteristics and usually has a poor prognosis. Early diagnosis is essential to determine and expand the patient's therapy.

Keywords: Diffuse meningeal melanomatosis; leptomeningeal melanoma; melanocyte; meninges; central nerve system.
PRIMARY DIFFUSE MENINGEAL MELANOMATOSIS – CASE REPORT


Palavras-chave: Melanomatose meníngea difusa; melanoma leptomeníngeo; melanócito; meninges; sistema nervoso central.

RESUMEN
Antecedentes: La melanomatosis meníngea difusa (MM) forma parte de un grupo de enfermedades melanocíticas raras. Con el objetivo de enfatizar aspectos de la historia natural, diagnóstico y tratamiento de esta rara enfermedad decidimos reportar el presente caso. Descripción del Cade: Chica de 17 años que consultó por cefalea durante los últimos 45 días, seguida de episodios de agitación y alucinaciones. La tomografía reveló un leve aumento meníngeo en el hemisferio derecho. La RM reveló engrosamiento difuso significativo de la duramadre, que invade la corteza cerebral y la sustancia blanca, incluyendo el tronco encefálico. El estudio del líquido cefalorraquídeo mostró la presencia de células neoplásicas, la citología confirmó la presencia de melanocitos. El estudio histológico, realizado a partir de la biopsia cerebral, mostró melanocitos difusos infiltrando las meninges, el espacio subaracnoideo y la corteza cerebral. El diagnóstico histológico fue MM difuso. Conclusiones: En conclusión, la MM difusa es una condición poco frecuente de características malignas y suele tener un mal pronóstico. El diagnóstico precoz es fundamental para determinar y ampliar la terapia del paciente.

Palabras clave: Melanomatosis meníngea difusa; melanoma leptomeníngeo; melanocito; meninges; sistema nervoso central.

1. Introduction
Primary melanocytic neoplasms of the central nervous system (CNS) are rare lesions.[7] They can be diffuse or focal, benign or malignant. They were first described in 1859 by Virchow.[7] According to the World Health Organization CNS tumors classification (2007), they are divided into diffuse melanocytosis, melanocytoma, primary malignant melanoma and meningeal melanomatosis (MM).[8]

In order to differentiate themselves as melanocytic neoplasms, it is necessary to recognize the specifications of tumor cells, which can present themselves as focal or diffuse lesions that arise from leptomeningeal melanocytes. Among diffuse lesions, MM differs from melanocytosis in that it
presents as malignant lesions that can be diffuse through non-metastatic invasion of leptomeninges, but also multifocal. [2]

Diffuse MM is a rare variant of CNS malignant melanoma [12] that occurs in 0.005 per 100,000 habitants, which makes it rare condition. [5,12] It is more frequent in adults than children, in whom sometimes it can be associated with pigmented, multiple or extensive skin injuries and often transmitted as autosomal dominant pattern. [9]

Given the rarity of this disease, we decided to this case report and review of the literature, with emphasis on natural history, diagnosis and treatment of these injuries.

2. Case Report

A 17 years-old white woman, presenting with a 45 days headache followed by episodes of psychomotor agitation and hallucinations was admitted. She had a progressive worsening of consciousness, difficulty to speak and weight loss. She was confused, with neck stiffness, bilateral abducent nerve palsy, a left side peripheral facial nerve palsy, dysphonia, decreased visual acuity bilaterally and tetraparesis with hypotonia and generalized hyporeflexia.

Computed tomography (CT) scan showed mild meningeal contrast enhancement on the right hemisphere. Magnetic resonance imaging (MRI) showed diffuse meningeal thickening extending to cortex and white matter [Figure. 1A], with contrast enhancement [Figure. 1B], including brain stem [Figure 1C]. On T1-weighted MRI revealing a high-intensity round homogeneous lesion at cranial base (melanocytoma) [Figure. 1D]. The cerebrospinal fluid (CSF) study showed yellowish aspect, glucose 44 mg/dl, protein 162 mg/dl, positive Pandy reaction (+), 26 cells (70% basophils with multinucleation and prominent nucleoli). Presence of neoplastic cells which cytopathology showed be melanocytes. The dosage of adenosine deaminase (ADA) in the CSF was normal. ELISA anti-HIV serology was negative.

We decided to perform a duramater and brain biopsy by a frontal craniotomy. The duramater presented an abnormally black/gray color [Figure. 2], however brain tissue macroscopically was normal. The histological study demonstrated diffuse melanocytes infiltrating the meninges in the subarachnoid.
space as well as brain cortex, confirming the diffuse MM diagnosis [Figure. 3].

Even considering her poor clinical conditions and prognosis, she was submitted to radiotherapy and chemotherapy. There was no improvement after the therapeutic intervention and the patient died eight months after diagnosis.

3. Discussion

Primary CNS melanocytic tumors are rare lesions derived from leptomeningeal melanocytes. [5] The presence of melanocytic cells in the CNS is justified by the neuroectodermal embryonic development of the neural crest, which consists of a structure formed by multipotent cells that appears around the 22nd and 23rd day of embryogenesis at the ends of the neural tube and differs in several cell types, including leptomeninges, glial cells, adrenal medullary cells and melanocytes. As the cerebral hemispheres develop and expand, they carry a thin layer of neural crest cells, or that results in the formation of leptomeninges that can be used as melanocytes. [7]

In exceptional cases, melanocytes can cause central primary melanoma of the CNS, that can be a solid tumor and diffuse meningeal melanomatosis. The diffuse shape represents infiltrations into the subarachnoid space and the surface parts of the brain without solid mass. May occur local nodular infiltration or meningitis, which is an extremely aggressive disease. [5]

Clinical diagnosis of primary diffuse meningeal melanomatosis is difficult, because can clinically mimic a wide variety of other conditions, including lymphoma, leukemia, metastatic carcinoma, subacute meningitis, viral encephalitis, and idiopathic hypertrophic cranial pachymeningitis. [9] The most common symptoms include headache (46%), nausea or vomiting (37%), back or neck pain (24%) and weakness (22%). Other features include hydrocephalus, seizures, ataxia, spine medullary cavity, cranial nerve palsy, intracranial hemorrhage and neuropsychiatric symptoms. [4,7] Meningeal melanomatosis affects the brain tissue in all cases described so far and spinal cord in 43% of cases. [5]

The differential diagnosis between melanocytic lesions is often confused due to its similar radiological appearance, so confirmation by electron microscopy and immunohistochemistry is desirable. [5] MM may be radiologically and clinically
confused with diffuse leptomeningeal neoplasms or with intracranial hypotension syndrome. [6] In the present case, both CT scan and MRI showed diffuse thickening and contrast enhancement of the meninges, confirming the same findings described in the literature. [3,7]

Leptomeningeal melanomatosis MRI aspects are strongly influenced by the paramagnetic effects of melanin. Therefore, they are generally hypointense in T2-weighted images and hyperintense in T1-weighted images with contrast enhancement. [12]

An increase in pressure can be observed during the lumbar puncture procedure in patients with diffuse MM [7] as low glucose and high lactate are nonspecific findings [12] and a brown color of the CSF is suggestive for melanomatosis. [5] Malignant cells are detected in the CSF in 50-70% of patients, a rate that increases to 80% with repeated sampling. [1]

Cerebral or meningeal biopsy is often the definitive diagnostic procedure. [9] Anatomopathological diagnosis is made by the presence of a brown pigmented lesion in the leptomeninges. [11] Immunohistochemical study shows a positive reaction to anti-melanoma antibodies (HMB-45), Protein S-100 and vimentin. [12]

Early diagnosis is important and gives the possibility to initiate the more appropriated treatment modality. [5] Dacarbazine combined with radiation and chemotherapy has recently proved to be the most effective treatment for melanomatosis. [5] Corticosteroids seems to be effective for symptomatic relief, but only prolongs survival two months. [12] Berzero et al proposes in his work an algorithm to guide and streamline the complex process of differential diagnosis of MM in order to allow better therapeutic options for the patient. [1]

Given the diffuse nature of MM, complete surgical resection is not possible. Systemic therapies such as radio, chemotherapy and immunotherapy have varying levels of success. Diffuse meningeal melanomatosis is generally relatively radioresistant with little response to radiotherapy. [10] However, cases have been reported with high response rates using high dose fractional doses radiation and combined chemotherapy. [10]

Currently, there are advances in studies with immunotherapy for the treatment of neoplasms. In a study published by Krpan et al (2020), a good response to the treatment of meningeal melanoma with the PD-1 protein inhibitor
antibody was demonstrated, which stabilized the disease for 2 years. It is a humanized monoclonal antibody called Pembrolizumab, with the function of inhibiting PD-1, a checkpoint protein of immune system cells, allowing a favorable result to antineoplastic activities. In our case, immunotherapy was not used, as it has not been evaluated at the time.

The prognosis of MM is poor, and the majority of untreated patients die within 1 to 9 weeks after diagnosis. Early diagnosis and initiation of therapy may have the potential to improve patient survival, especially in metastatic tumors. In our report, the patient survived for 8 months after diagnosis through supportive therapies associated with radio and chemotherapy.

4. Conclusion

Diffuse MM is a rare disease with just a few reported cases that is still a challenge for neurosurgeons and neuro-oncologists. Therefore, the prognosis is generally poor and severe. Immunotherapy, chemotherapy and radiotherapy must be considered on treatment plan and will define patient's outcome. Early diagnosis is essential to treatment.

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REFERENCES


ANNEX

Figure 1. T1-weighted MRI revealing a low-intensity asymmetry at right brain hemisphery. (a) Addition of gadolinium yielded enhancement involving dura, subarachnoid space and cerebral cortex. (b) And brain stem dura. (c) T1-weighted MRI revealing a high-intensity round homogeneous lesion at cranial base (melanocytoma). (d)

Source: own authorship
Figure 2. Peroperative black/gray color duramater aspect during biopsy by a frontal craniotomy

Source: own authorship

Figure 3. Photomicrograph demonstrating diffuse melanocytic cells infiltrating dura-mater subarachnoid space and even cerebral cortex (H & E).

Source: own authorship