mology department, so a diagnosis of HvCJD should be taken into consideration.

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Primary diffuse leptomeningeal melanomatosis: Description and recommendations

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ABSTRACT

Primary melanocytic disease of the central nervous system is a rarely encountered condition currently without consensus on treatment and lacking major guidelines for management. Understanding the nature of the disease and differentiating primary melanocytic disease from the much more commonly encountered secondary (metastatic) melanoma is important in identifying the condition and pursuing appropriate treatment.

1. Introduction

Melanocytic disease of the central nervous system is most often encountered in the setting of metastatic melanoma, a clearly pathological condition. Management strategies for this common presentation of melanoma are well established. Much more rarely encountered, and the focus of this review, is the clinical finding of primary melanocytic conditions of the central nervous system (CNS), which can present with symptoms or be incidentally detected without clinical correlate. Primary melanocytic disease of the CNS can be benign or extremely pathologic, or somewhere in between. Familiarity with the spectrum of melanocytic conditions of the CNS, their origins, and management of potential sequelae is important for clinicians who may encounter them.

Our goal in this review is to present a representative example of one of these conditions and its management, followed by a discussion into the origin of primary melanocytic conditions. We thoroughly describe multiple known primary melanocytic conditions, both benign and pathological, and their management strategies as currently described in the literature.

2. Case report

2.1. History and presentation

A 71-year-old female with a history of a non-invasive papillary bladder carcinoma developed left hemibody numbness, as well as mild left-sided weakness. She was referred to neurology for initial management. Further history revealed complaints of a recent onset of daily headaches, word-finding difficulty, and increasing difficulty with balance. Physical examination revealed bilateral 5/5 strength in upper and lower extremities with no pronator drift. Sensory examination showed diminished sensation to pain and light touch on the left side. Brain magnetic resonance imaging (MRI) demonstrated multiple nodular enhancing foci (Fig. 1). Initial management was frequent monitoring and serial MRIs. Several months after initial evaluation, the patient presented to the emergency room with new-onset confusion. Computed tomography (CT) revealed new-onset hydrocephalus, and a ventriculoperitoneal shunt was placed. Following recurrent confusion and new-onset diplopia, craniotomy for open biopsy was planned for tissue diagnosis.

2.2. Operation

In the operating room, a 3 × 3-cm bone flap was opened. Following dural opening, diffuse melanotic deposits were immedi-

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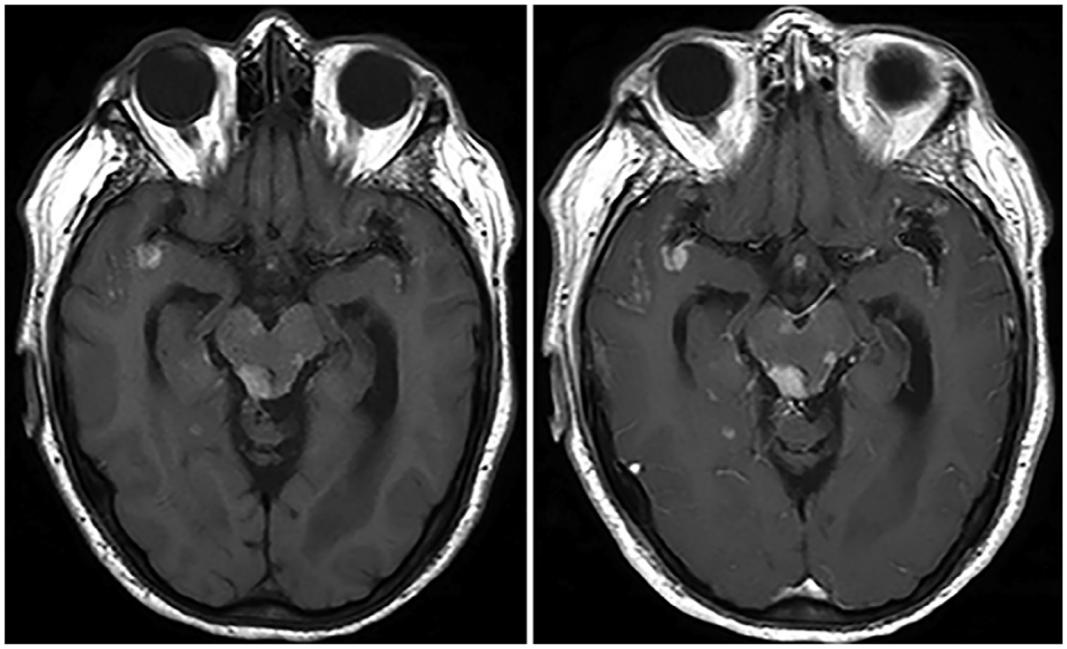

Fig. 1. Multiple intra-axial T1 hyperintense lesions visible in the bilateral insula, tectal region, cisterns, and along the midbrain. T1 sequences without (left) and with (right) contrast.

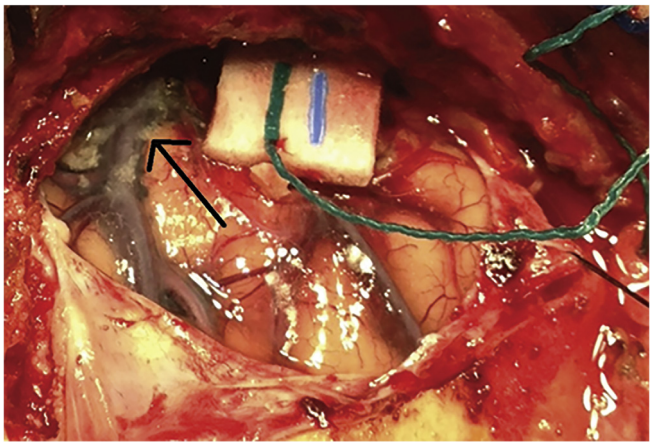

Fig. 2. Darkly pigmented melanotic deposits visible in the subarachnoid space after dura was opened and reflected.

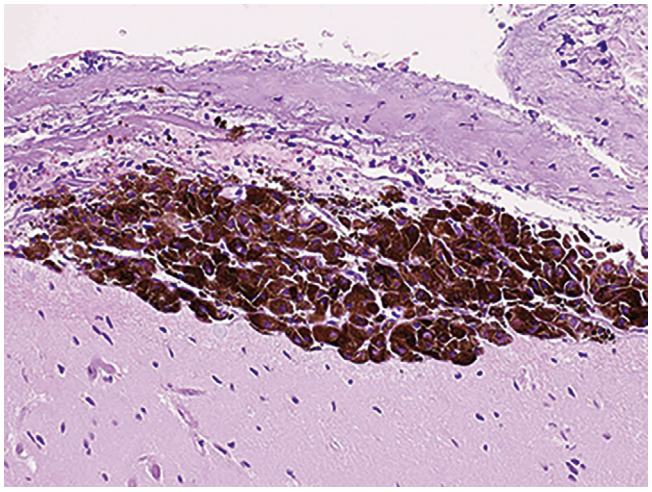

Fig. 3. A cluster of leptomeningeal cells contains numerous small, dark brown cytoplasmic melanin pigment granules. Most individual melanin granules are smaller than 3 μm in diameter. The dark pigment obscures nuclear details.

ately encountered in the subarachnoid space (Fig. 2). Several biopsies were collected for pathologic examination.

2.3. Pathologic findings

On histopathologic examination, the right temporal mass showed a leptomeningeal collection of large epithelioid cells that contained abundant darkly pigmented granules (Fig. 3). To reveal the cytologic detail of these cells, a permanganate bleaching procedure was performed (Fig. 4). The cells had round to ovoid nuclei with finely speckled chromatin, moderately-sized nucleoli, minimal cytologic atypia, and rare cytoplasmic inclusions. Mitotic activity was inconspicuous. The cells were positive for Melan A and were thus consistent with melanocytes. The proliferative index (Ki-67) was between 1 and 2%. Molecular testing for BRAF V600E/V600K and KIT mutations was negative. Depending upon the clinical context and extent of disease, these findings would be consistent with either melanocytoma or diffuse leptomeningeal melanomatosis. There was no evidence of parenchymal invasion or leptomeningeal spread and invasion into Virchow Robin spaces.

2.4. Postoperative course

Following her biopsy and diagnosis, the patient was referred to radiation and medical oncology for management of workup of metastatic melanoma. Dermatology evaluation revealed no skin lesions. Whole-body PET scan revealed no other areas of avid uptake. Workup of breast mass and fine-needle aspiration of thyroid nodule did not reveal other foci of disease. MRI of total spine was performed to assess for further central nervous system (CNS) involvement and revealed leptomeningeal involvement of the spinal cord and cauda equina. Given the absence of a primary mel-

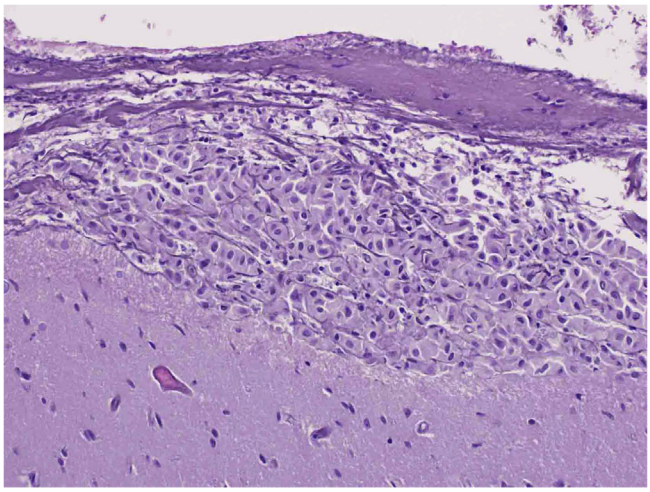

Fig. 4. Melanin pigment can be bleached by permanganate. Bleaching uncovers cytologic atypia, which is less than seen in melanoma. Mitotic figures are inconspicuous. Nuclei are predominantly round-to-oval with finely speckled chromatin, some of which accumulates along the nuclear membrane. There are small- to moderate-sized nucleoli and rare cytoplasmic nuclear inclusions. These are cellular and nuclear features of leptomeningeal melanocytosis. Hematoxylin and eosin staining; 200× magnification.

anocytic focus outside the CNS and the leptomeningeal location of the patient's disease, primary leptomeningeal melanomatosis was suspected. Fractionated whole-brain radiation therapy was performed with a total of 37.5 Gy administered. Her condition was deemed to be too debilitated to tolerate systemic therapy. Patient continued to have cognitive and functional decline, with a progressive loss of orientation, interactivity, speech, and inability to perform the basic activities of daily living. Hospice care was eventually recommended given her poor prognosis and severe progressive disability.

3. Discussion

Primary melanomatous disease of the central nervous system is a rare yet diverse disease with a spectrum of malignancy and presentation. Primary leptomeningeal melanomatosis occurs in 1 in 10–20 million people [1,2]. The disease is believed to arise from melanotic cells of the CNS, melanoblasts, which are of neural crest origin. The neural crest is an ectodermal derivative which gives rise to structures of the central and peripheral nervous system and a number of other structures, including the leptomeninges, the cerebral vasculature, and elements of the cranial bones and cartilage. For this reason, although primary CNS melanocytic neoplasms are thought to arise from a common cellular origin, they have diverse presentations due to their potential to arise at virtually any site of neural crest origin that contains melanocytes. Reports exist that describe primary leptomeningeal melanoma originating from multiple sites, including the cerebral convexities, the midbrain, the cerebellopontine angle, the cerebellum, the suprasellar region, and the spinal cord. Current thought is that primary CNS melanocytic tumors arise from melanotic cells of neural crest origin.

Melanocytic disease within the CNS can be categorized as primary or secondary. Secondary melanocytic disease is more commonly referred to as metastatic melanoma, which is the nomenclature we will use for the remainder of this article. Melanocytic disease more commonly occurs secondary to melanomatous lesions elsewhere in the body. Metastatic melanocytic disease of the central nervous system is usually a marker of systemic disease and heralds a poorer prognosis. Primary melanocytic disease of the CNS occurs rarely compared to secondary disease, and diagnosing primary disease requires that lesions elsewhere be ruled out with a comprehensive skin examination and an ophthalmologic evaluation.

The 2007 World Health Organization (WHO) classification of tumors of the central nervous system describes several types of proliferations of leptomeningeal melanocytes [3,4]. These neoplasms may be circumscribed or diffuse. The former include melanocytoma, intermediate-grade melanocytic tumor, and melanoma, while the later consist of melanocytosis and melanomatosis.

Melanocytomas are slow-growing neoplasms, the gross appearance of which varies from black to red-brown to amelanotic nodules. Microscopically, they generally consist of bland pigmented epithelioid cells with minimal cytologic atypia, rare mitoses, and a low proliferative index. Up to half of melanocytomas have been reported to recur [3]. When possible, they should be completely resected. Resection is not possible in cases with leptomeningeal seeding. In such cases, adjuvant radiation therapy is advised. In contrast, melanomas are frankly malignant neoplasms composed of pigmented epithelioid to spindled cells with mild to severe cytologic atypia, mitoses, and a high proliferative index. A third, loosely defined, circumscribed neoplasm, termed intermediate-grade melanocytic tumor, has also been described. This entity has histologic features intermediate between melanocytomas and melanomas.

Melanocytosis is a diffuse proliferation of histologically benign-appearing leptomeningeal melanocytes that shows no frank invasion of the underlying central nervous system parenchyma. Even without histologic malignancy, diffuse melanocytosis has a poor prognosis [4]. Melanomatosis refers to the aggressive spread of malignant, atypical melanocytes through the leptomeninges and often into the adjacent brain parenchyma.

Primary CNS melanocytic neoplasms can be categorized by location into two groups, leptomeningeal and parenchymal, and further characterized into benign and malignant groups. Leptomeningeal melanocytic conditions include meningeal melanocytomas (benign), leptomeningeal melanosis (benign), and leptomeningeal melanomatosis or melanoma (malignant). Leptomeningeal melanomatosis can be of two subtypes: diffuse or nodular. Parenchymal melanocytic disease includes melanocytoma (benign) and primary CNS melanoma (malignant).

3.1. Leptomeningeal melanosis

Leptomeningeal melanosis is a benign primary melanocytic condition of the central nervous system that results in benign hyperpigmentation of the pia and arachnoid of the brain or spinal cord. It is usually an asymptomatic condition that is incidentally detected on imaging, and frequently occurs alongside cutaneous conditions such as giant congenital melanocytic nevi. Brain MRI on pediatric subjects with congenital melanocytic nevi detected leptomeningeal melanosis in 6–20% of patients [5,6].

On follow-up of patients with asymptomatic leptomeningeal melanosis, the overwhelming majority remained asymptomatic; however, 2–3% developed neurological symptoms and about half of those patients showed evidence of malignant transformation to melanoma [7,8].

3.2. Leptomeningeal melanomatosis (leptomeningeal melanoma)

Leptomeningeal melanomatosis is a malignant condition that results from the diffuse invasion of melanocytes into the leptomeninges, without parenchymal invasion [9]. Leptomeningeal melanomatosis can be either diffuse or nodular, with nodular disease occur frequently in the posterior fossa [10].

Leptomeningeal melanomatosis results due to spread into the subarachnoid space by a meningeal melanoma [9,11–13]. Leptomeningeal melanomatosis is also described in the literature as leptomeningeal metastasis from malignant melanoma, and has been associated with poorer outcomes [14]. Primary meningeal melanoma is usually a solitary malignant lesion with the potential to metastasize, and leptomeningeal melanomatosis can occur due to metastasis of a meningeal melanoma to the leptomeninges. Leptomeningeal melanomatosis can also occur with malignant transformation of leptomeningeal melanosis, as discussed above.

Diffuse melanocytic conditions of the central nervous system have an association with dermatologic conditions, such as neurocutaneous melanosis [12]. Approximately a quarter of patients with leptomeningeal melanoma have been reported to have an associated cutaneous congenital pigmented nevus [15]. One particularly notable nevus associated with leptomeningeal melanomatosis is the nevus of Ota, which occurs on the face and eyelid unilaterally and frequency involves the sclera and choroid of the eye [16].

3.3. Melanocytoma—meningeal or parenchymal

Primary CNS melanocytomas are benign melanocytic neoplasms that are usually meningeal in origin, though they can rarely be parenchymal. These lesions usually present as a single nodular black mass that does not invade local structures [4]. Melanocytomas are solitary, well-differentiated masses that are usually curable with primary resection [17], although they exist on a spectrum between benign and malignant and at times have been known to recur and sometimes undergo malignant transformation [18]. Melanocytomas most often occur in the leptomeninges, but they can rarely arise from the parenchyma, especially in association with syndromes such as neurocutaneous melanosis [19].

3.4. Primary CNS melanoma

Primary CNS melanoma is malignant melanocytic disease of the central nervous system. It may arise anywhere in the central nervous system, though a predilection for the posterior fossa and spinal cord has been noted [12]. It is a malignant tumor with the ability to metastasize, usually to the leptomeninges but to other organs as well [13].

The prognosis of primary CNS melanoma can be favorable, especially as compared to metastatic CNS melanoma, which usually has a prognosis of less than 1 year [20]. Primary CNS melanoma has had survival rates reported in the range of years, with some case reports reporting survival greater than 10 years following surgical resection [21,22].

3.5. Natural history

Primary diffuse leptomeningeal melanomatosis has a wide spectrum of initial presentation, with symptoms ranging from mental status changes to focal neurological deficits. It is characterized by marked progressive clinical deterioration over the course of months to a year.

Patients with primary diffuse leptomeningeal melanomatosis generally follow a three-phase pattern of neurological decline. Initial presentation generally occurs with new-onset neurological deficits. About half of affected patients present with general symptoms of nausea, vomiting, and headache. Less commonly, patients present with confusion or deficits, including diplopia, weakness, gait changes, back or neck pain, bowel or bladder dysfunction, or sensory loss. Most patients eventually develop hydrocephalus, and their second period of neurological decline occurs with hydrocephalic symptoms [23]. Finally, even in the setting of shunted hydrocephalus, affected patients experience continual cognitive and motor decline as the primary pathologic process continues to progress.

Life expectancy following diagnosis of primary diffuse leptomeningeal melanomatosis ranges from months to a few years [24]. A case series by Kiel et al. [25] reported a range of survival time from 6 weeks to 7 years, with a median survival time of 5 months. However, there are several reports of longer survival times, usually associated with an unusually brisk response to therapy [1,11,26–30]. Kumagai et al. [29] reported survival time of greater than 12 years following surgical therapy. Nakagwa et al. [30] reported 9 years following resection and successful use of combined therapy when there was a recurrence.

3.6. Management

Initial management of primary leptomeningeal melanomatosis should focus on management of acute symptoms, particularly in the setting of hydrocephalus. Early diagnosis and initiation of therapy may have the potential to improve survival, as smaller tumor burden has been shown to improve survival in leptomeningeal metastases involving other tumors [31,32].

Definitive diagnosis of primary leptomeningeal melanomatosis is usually achieved with biopsy. Cerebrospinal fluid cytology by lumbar puncture can diagnose the condition if neoplastic melanotic cells are discovered, however there are reports in the literature of false negative findings [9]. Radiographic findings usually involve leptomeningeal enhancement, a relatively nonspecific finding. If tissue biopsy is not an option, cerebrospinal fluid cytology with detection of neoplastic melanotic cells, exclusion of the presence of potential sources of metastatic melanotic disease via comprehensive skin and ocular exam, and findings of leptomeningeal enhancement are an acceptable alternative means of diagnosis [33].

Meningeal melanomatosis is commonly complicated by the development of hydrocephalus, due to disruption of cerebrospinal fluid absorption by tumor infiltration of the leptomeninges. Palliative ventriculoperitoneal shunt placement is indicated in the setting of hydrocephalus to relieve symptoms. Consideration should be given to use of a filter with the shunt system to prevent seeding to peritoneum. Seeding to the peritoneum has been more frequently reported in neurocutaneous melanosis–associated leptomeningeal melanomatosis [34]; seeding has been reported with primary leptomeningeal melanomatosis as well [35,36].

Given the diffuse nature of leptomeningeal melanomatosis, complete surgical resection is not possible. Surgical therapy is limited to palliative debulking and shunt placement, as described above.

Systemic therapies such as radiation, chemotherapy, and immunotherapy have all been attempted for leptomeningeal malignant melanoma with varying levels of success. Generally, malignant melanoma has been found to be relatively radioresistant with little response to radiotherapy [37,38]. However, higher response rates have been reported with the use of high-dose fractionated radiation [39,40] and with combination chemotherapy [30]. Most published reports on the treatment of leptomeningeal melanomatosis focus on metastatic melanotic disease due to its higher prevalence, however a few reports on primary leptomeningeal melanosis exist [27,41]. According to a larger review study on metastatic leptomeningeal melanomatosis, prolonged survival was found with radiation therapy, chemotherapy, and immunotherapy, though the beneficial effect of immunotherapy was the only one to persist after multivariate analysis [11,14,42]. A review of metastatic leptomeningeal melanomatosis found that intrathecal chemotherapy was most effective in impacting sur-

vival, although primary leptomeningeal lesions were excluded from the review [14].

A case report on interleukin-2 therapy injected intrathecally into the lumbosacral space demonstrated survival at 15-month follow-up without development of new neurological deficits [27]. Intrathecal interleukin-2 has also been used, with positive results, as a therapy for metastatic leptomeningeal melanomatosis [41]. Other therapeutic agents for metastatic leptomeningeal melanoma that may have potential for eventual use in the treatment of primary diffuse leptomeningeal melanomatosis include IFN-alpha [43,44], temozolamide [45], dacarbazine [45], and ipilibumab [46].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jocn.2018.01.052.

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