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Case Report

Primary leptomeningeal melanoma in association with neurocutaneous melanosis: A case report

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ABSTRACT

Background: Primary melanocytic tumors of the central nervous system accounts for approximately 1% of all melanoma with a peak incidence in the fourth decade. The tumor originates from leptomeningeal melanocytes with a variable degree of belligerence. The proliferation of these melanocytes in large amounts in the dermis and nervous system can raise suspicion of neurocutaneous melanosis (NCM), which is an association between malignant melanoma and the presence of a giant intradermal nevus.

Case Description: We present a case of a 62-year-old South Asian male with a large congenital melanocytic nevus (>20 cm in size) in the left hemifacial, and head region who presented with complaints of a single episode of grand-mal seizure followed by neuropsychiatric symptoms. The patient was thoroughly evaluated both clinically and surgically leading to a rare diagnosis of primary leptomeningeal melanoma of the left temporal lobe. The patient subsequently underwent a neuronavigation guided left temporal craniotomy with gross total resection of the lesion.

Conclusion: Primary leptomeningeal melanoma with a clinical association with NCM is rarely ever reported within the literature. To date, our case is one of the very few instances where such an association is being reported in this age group along with rare neuropsychiatric symptoms.

Keywords: Leptomeningeal melanoma, Neural crest, Neurocutaneous melanosis, Nevus, Primary melanoma, Seizures

INTRODUCTION

Primary central nervous system (CNS) melanomas are malignant melanocytic lesions of the CNS that have a high metastatic potential. They are rare entities and comprise approximately 1% of all cases of melanomas and 0.07% of all brain tumors.[3] These lesions arise from melanocytes that are normally present in the CNS. They tend to occur in the 4th–5th decades of life.[12,13] Melanocytes have a neural crest origin,[17] after which they migrate during embryonic development, incorporating into the skin, uvea, cerebral parenchyma, leptomeninges, and mucous membranes.[14]

Primary CNS melanomas are clinically and histologically unique from their cutaneous and retinal counterparts. They demonstrate a benign clinical course.[9] They arise from the melanocytes

normally present in the leptomeninges. Radiologically, a melanocytic lesion in the CNS can be subclassified into either a diffuse type, characterized by having infiltrations into the subarachnoid space or a focal type of tumor.[14] Furthermore, malignant melanoma is closely related to congenital intradermal nevus, an association that exists in 40–60% of cases of neurocutaneous melanosis (NCM) disorder.[16] This association was described by Fox and later revised by Kadonaga and Frieden. However, the majority of the patients with NCM present with neurological deficits within the early 2 years of life.[10]

CASE PRESENTATION

A 62-year-old man presented to the emergency room after one episode of a generalized tonic-clonic seizure preceded by an aura of generalized body numbness and right hemiparesis. The family later reported a 3-week history of depressed mood, personality changes, and short-term memory disturbances. The patient had no previous history of seizures, trauma, or any other neurological symptom. He had recently been diagnosed with diabetes mellitus, gastroesophageal reflux disease, and depression. His medications included sitagliptin, metformin, omeprazole, and risperidone.

A detailed physical examination revealed a large congenital melanocytic nevus of more than 20 cm in size. The giant nevus was distributed unilaterally across the left side of the patient's face and head in a nondermatomal fashion [Figure 1]. Neurologically, his cranial nerves and higher mental functions were intact and he had no sensory, motor deficits, or cerebellar defects.

Subsequently, brain magnetic resonance imaging (MRI) showed a left temporal lesion in close approximation to the greater wing and petrous portion of the sphenoid bone and measured approximately 37 × 41 × 32 mm [Figure 2]. The lesion also resulted in the obscuration of the temporal horn of the left lateral ventricle with mild uncal herniation. It was hyperintense on the T1-weighted images and isointense on the T-2 weighted images with perilesional edema and areas of signal dropout on susceptibility-weighted imaging. Computed tomography of the chest, abdomen, and pelvis was performed to look for any systemic involvement and was unremarkable.

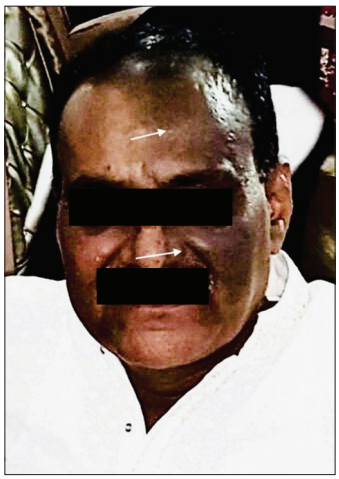

Figure 1: Cutaneous pigmentation (white arrows) of the periorbital and malar region on the unilateral left side of the face head in a nondermatomal fashion.

A standard left temporal craniotomy was performed during which the tumor was recognized as a darkly pigmented mass in the anteromedial aspect of the left temporal lobe. The tumor was pigmented and firm. It was surrounded by a blood clot of variable ages and was separable from the brain parenchyma. During the procedure, patchy pigmented leptomeninges, islands of pial pigmentation, and perivascular dark arachnoid deposits were also noticed [Figure 3]. Gross total resection (as confirmed by postoperative MRI) was performed and the patient was discharged on the 3rd postoperative day after smooth postoperative recovery.

On histopathology, the tumor was revealed as a neoplastic lesion consisting of cells arranged in a solid sheet pattern. The cells individually possessed scanty cytoplasm, an abundance of dark brown pigment coupled with enlarged hyperchromatic round nuclei and prominent nucleoli. Moreover, scattered mitotic activity and reactive glial tissue were also highlighted. Immunohistochemical stains were performed which showed a reactivity pattern consistent with melanoma; Melan A Positive, HMB45 Positive with Ki-67 high proliferative index [Figure 4].

Postoperatively, a multiplanar and multi sequential MRI of the brain was performed with and without IV

gadolinium contrast that showed no post-contrast enhancement or visualization at the site of the previously seen lesion to suggest residual disease. He had a stable postoperative course and was discharged on tapering doses of steroids and anti-epileptics. His case was discussed in our multidisciplinary tumor board meeting and was referred to a medical and radiation oncologist for adjuvant therapy.

DISCUSSION

Melanocytes are pigment cells in the CNS that are normally localized in the pia mater, high cervical cord, and the frontal part of the medulla oblongata. One theory has described that the pigment cells have a neural crest origin, which eventually develops into mesodermal and neural elements and gives rise to tumors.[15] The tumor cells can spread to the leptomeninges such as the arachnoid and pia mater, and become visible as either discrete dots or clusters of branching pigmentation.[8] Primary CNS melanomas are characterized by the absence of

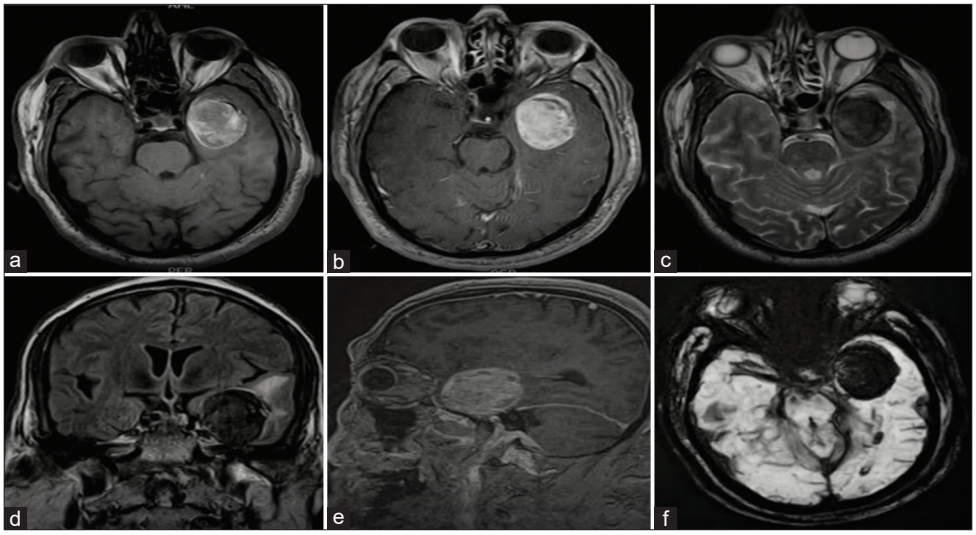

Figure 2: Preoperative multiplanar and multisequential MRI of the brain. (a) T1 without contrast shows a heterogeneous hyperintense lesion in the left temporal region, (b) T1 with contrast shows further enhancement on contrast administration, (c) T2 shows a hypointense lesion with surrounding hyperintense signals, (d) fluid-attenuated inversion recovery showing edema surrounding lesion, (e) T1 post contrast sagittal, and (f) susceptibility weighted image displaying areas of signal drop out.

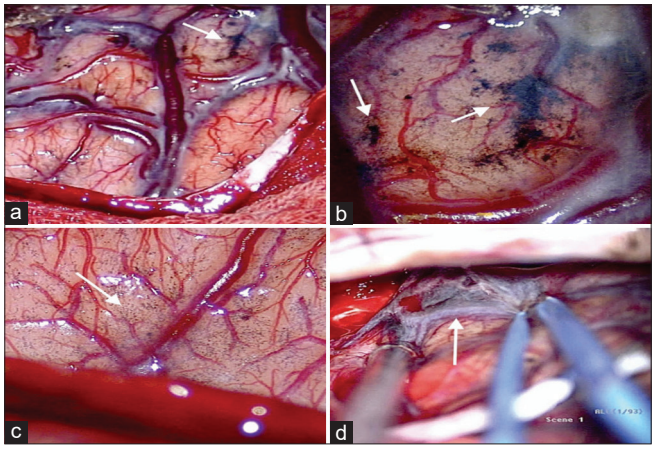

Figure 3: Surgical images of densely pigmented leptomeninges of the brain, as seen under the operating microscope. (a and b) Pattern of black multiple discrete clusters of hyper-pigmentation seen over the brain meninges (white arrow). (c) Extensive pigmentation seen as a sheet of dots spread over the leptomeninges (white arrows). (d) Dark, blotched, and pigmented vascularized (white arrows) meninges.

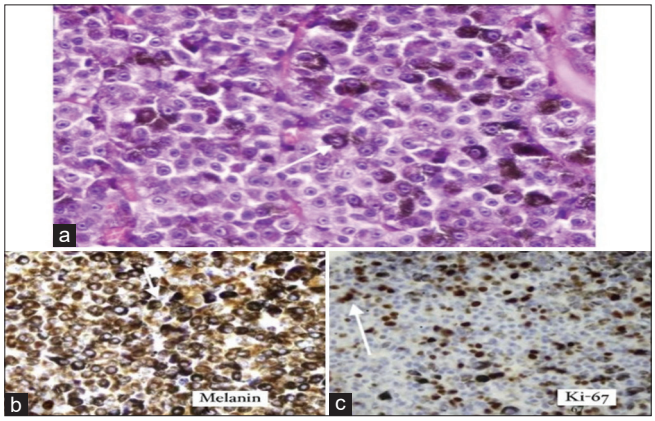

Figure 4: Histopathology of primary leptomeningeal melanoma. (a) Hematoxylin and Eosin stained sections show sheets of medium-sized polygonal cells with moderately pleomorphic nuclei (white arrows) containing dispersed chromatin, macronucleoli, and moderate amounts of eosinophilic cytoplasm. (b) Immunoperoxidase staining for Melan A shows diffuse cytoplasmic staining (white arrows) in tumor cells. (c) Positive staining for Ki-67 (white arrows) is observed.

melanocytic lesions outside the CNS along with histological confirmation. For comparison, metastatic melanomas are differentiated from primary lesions by findings of multiple intracerebral lesions, having a rapid and poor clinical course, and their appearance in relatively older patients.[20]

NCM is described as a neuroectodermal dysplasia, characterized by large (>20 cm) or multiple congenital nevi associated with meningeal melanosis or melanoma. The diagnosing criteria also include the following two clinical aspects: no evidence of cutaneous melanoma except in patients in whom the examined areas of the meningeal lesions are histologically benign; no evidence of meningeal melanoma except in patients in whom the examined areas of cutaneous lesions are histologically benign.[6] Our patient had a large benign congenital nevus on one half of the face. On MRI, our patient was seen to have a paramagnetic lesion, which was confirmed to be a primary CNS melanoma, with no evidence of metastasis from any other area of the body. Therefore, he fulfilled the criteria to be diagnosed as a case of NCM. The uniqueness of our case, however, lies

Table 1: Shows the treatment combinations used in various diffuse and focal leptomeningeal melanomas reported with/without benign congenital nevus and their outcomes.

S. No.	Age	Gender	Site of CNS melanoma	Site(s) of congenital nevi (if present)	Immunoreactivity	Diagnosis	Treatment(s)	Outcome
1 (18)	13 years	Male	Left temporal, and smaller lesions in the left parietal lobe and cerebellum	Absent	Malen A (+), and HMB45 (+)	Primary diffuse leptomeningeal melanomatosis	Surgical excision	Death within 5 months
2 (12)	30 years	female	The left frontal region, leptomeningeal spread in the subarachnoid space from the level of C2-C3	Multiple on trunk, thoracodorsal region (32 cm × 20 cm), left thigh ((25 × 18 cm), cephalic ((5 cm × 4 cm)	S100(+), HMB45(+), MelanA(+), and MiTF(+)	Neurocutaneous melanosis	Radiotherapy (40 Gy dose) and chemotherapy (temozolomide 200 mg)	Multiorgan failure and death
3 (13)	72 years	Female	Inferior gyrus of the right frontal lobe	Absent	melan A (+), HMB45 (+), and S-100(+)	Primary leptomeningeal melanomatosis	Radiotherapy (30 Gy dose) and chemotherapy (pembrolizumab 2mg/kg every 3 weeks)	Alive at 3 year follow-up but has experienced neurological worsening.
4 (19)	35 years	Female	Left temporal lobe along the sylvian fissure	Absent	HMB-45(+), Melan A (+), S-100 (+), VEGF(+),GFAP (+)and Vimentin(+)	Primary cerebral melanoma	Surgical excision and radiochemotherapy (concomitant stereotactic radiosurgery + temozolomide)	Good recovery at 11 month follow up
5 (20)	53 years	Female	Pineal region	Absent	S-100 (+)	Primary pineal melanoma	Partial surgical removal followed by chemotherapy (dacarbazine, 150 mg/day intravenously for 5 days; vincristine,.	Follow-up for 4 years showed good recovery
6 (21)	17 years	Male	Posterior fossa with diffuse leptomeningeal melanocytosis of the spine	Muliple hairy nevi over the body, largest measuring 10 × 5 cm over the back	S-100 (+), HMB-45 (+)	Neurocutaneous melanosis	Surgical excision and radiotherapy (dose of 2Gy/ fraction, 18 fractions)	Developed quadraplegia and intradural metastasis
7 (22)	46 years	Male	Right temporal lobe and diffuse melanosis of leptomeninges	Multiple nevi of on the back, buttocks, right sole, and limbs	S-100 (+), and HMB-45 (+)	Neurocutaneous melanosis	Surgical excision and radiotherapy.	Death within one month with deterioration of respiration, anisocoric pupilary response and coma.

CNS: Central nervous system, HMB45: Human melanoma black-45, MiTF: Melanocyte inducing transcription factor, Gy: Gray, VEGF: Vascular endothelial growth factor

in the fact that symptoms of NCM are majorly present in the first 2 years of life,[5] characterized by high intracranial pressure, hydrocephalus, cranial nerve palsy, hemiparesis, developmental delays, and seizures.[10] Our patient had only one episode of seizure at the age of 62, with psychiatric symptoms for years. It is very rare for NCM to present at a later age like in this patient. His neuropsychiatric symptoms are, however, consistent with the manifesting symptoms of NCM that are found in later years of life.[2]

CNS melanomas have a nonuniform histological pattern and are divided into four subtypes; the majority of the tumors are: (1) epithelioid,[9] however, (2) pleomorphic, (3) spindle-shaped,[11] and (4) mixed cell types are also found.[7] Primary leptomeningeal melanomas also show cellular pleomorphism, mitoses, necrosis,[4] and hemorrhage. Immunocytochemical tests aid in the diagnosis of these tumors. S-100 is a non-specific marker of melanomas as it also stains positive for gliomas and meningiomas. HMB-45 positivity has a higher specificity for melanomas.[12] However, unlike meningioma, CNS melanocytic lesions are usually negative for epithelial membrane antigen.[3]

Computed tomography (CT) is of limited diagnostic value for these tumors that produce isodense or hyperdense lesions.[14] Melanocytes demonstrate paramagnetism, causing shortening of both the T1 and T2 relaxation times. They appear as hyperintense and hypointense on T1- and T2-weighted imaging, respectively.[5] On postprocessed susceptibility-weighted images, signal dropout and blooming would be expected in the presence of diamagnetic (calcification) and paramagnetic (hemosiderin) properties. However, to distinguish between microhemorrhages in melanoma and calcification in meningioma, phase-filtered images are useful. They would show calcification as a hyperintensity due to a negative phase shift and loss of signal for hemosiderin due to a positive phase shift.[1] CT can also confirm the calcification in meningiomas. Although CT was not performed in our case, our patient had a left temporal lesion that was hyperintense on T1-weighted images and hypointense on T2-weighted images. Areas of signal dropout were seen on SW-images which signified microhemorrhages.

Treatment options for primary CNS melanoma include surgical excision which carries a good outcome, compared to radiotherapy and chemotherapy, which can be used as adjuvants.[18] Radiation can be given as whole-brain radiotherapy, or just involved-field radiotherapy at the site of the bulky lesion.[3] One patient underwent whole-brain radiotherapy with intra-CSR chemotherapy. Methotrexate (MTX) 15 mg and dexamethasone 5 mg were administered intrathecally for 8 weeks providing complete remission. However, the patient was required to undergo monthly intra-CSF chemotherapy and noncompliance was eventually the cause of her death.[14] Other chemotherapeutic drugs that can be administered include MTX, dacarbazine, vincristine, temozolomide, and interferon, although due to the rarity of these tumors, no standardized guideline for treatment exists.[19] Table 1 further shows the reported treatment combinations used for melanoma and their outcomes.

Malignant manifestation of a primary CNS lesion without metastasis, in juxtaposition to congenital nevi in an older patient, is a unique rarity in clinical neuromedicine. What provides significance to our report is the rare presentation of lesions, late onset of symptoms, importance of neuroimaging, and prompt surgical approach that prevents tumor spread and ensures the longevity of life.

CONCLUSION

The peculiarity of our case lies in the fact that NCM was discovered late in a 62-year-old patient with neuropsychiatric symptoms, providing an addition to the rarity of such cases found in the literature. The presence of a giant nevus along with a malignancy in the CNS should raise the suspicion of NCM regardless of the age of a patient.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest

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