

## Aggressive Primary Pediatric Intracranial Malignant Melanoma: Sphinx of the Tissue Diagnosis

### Abstract

It is often intriguing to suspect and confirm the diagnosis of primary malignant melanoma (PMM) in the brain without any evidence of neurocutaneous melanosis. We report a 16-year-old male patient with malignant melanoma which intraoperatively was small sized, soft, fleshy, hemorrhagic in appearance resembling hematoma. Interestingly, the histopathology showed prominent papillary architecture with a differential diagnosis of papillary meningioma and ependymoma and perplexed the tissue diagnosis. This case is discussed in light of very uncommon occurrence of intracranial PMM in pediatric age group, enigmatic histological features, and aggressive nature of lesion with rapid progression despite complete excision following radiation therapy.

**Keywords:** Immunohistochemistry, intracranial, paediatric, primary malignant melanoma, prognosis

### Introduction

Malignant melanoma (MM) is a potentially life-threatening neoplasm that develops from specialized pigment cells called melanocytes.<sup>[1]</sup> Primary malignant melanoma (PMM) in the brain in the pediatric age group is not often reported and detailed in the literature.<sup>[2-5]</sup> It is often described in association with cutaneous melanosis.<sup>[1,6]</sup> In the central nervous system (CNS), melanoma is often described in relation to leptomeninges termed as leptomeningeal melanosis.<sup>[7]</sup> The imaging or histopathological features with recent advances in the immunohistochemical markers do not contribute to distinguish primary from metastatic melanomas that made these patients to undergo thorough investigation.<sup>[2,6]</sup> The lack of guidelines regarding adjuvant treatment in dealing with these tumors results in poor outcome with inevitable recurrences despite complete surgical excision.<sup>[3]</sup>

### Case Report

A 16-year-old male patient was presented with headache and vomiting for 2 months. He developed left upper and lower limb weakness for 15 days. There was no history of immune suppression, family history of melanoma, or nevus or sunburns. His

general examination did not reveal any nevus. Neurological examination revealed bilateral papilledema and Grade 4 power in the left upper and lower limb.

Computed tomography (CT) plain imaging showed cortical based hyperdense lesion measuring 26 mm × 26 mm in the right parietal region. It was associated with bleed measuring 48 mm × 38 mm. [Figure 1a] Magnetic resonance imaging (MRI) showed well-circumscribed, lobulated, cortical-based lesion with bleed in the right parietal region. It measured 26 mm × 26 mm × 18 mm in size. It was isointense to gray matter on both T1, T2W images and mildly hyperintense on fluid-attenuated inversion recovery images. Diffusion-weighted images (DWI) showed irregular peripheral restriction of the lesion and susceptibility on susceptibility-weighted images. Heterogeneous enhancement on contrast images was noted. The lesion was associated with varying ages of bleed measured 48 mm × 42 mm × 34 mm. The bleed showed intense hyperintensity on T1W images and iso- to hyper-intense on T2W images. There was perilesional edema with midline shift of 5 mm. Magnetic resonance (MR) angiography showed normal flow signals within the intracranial arteries. No other abnormality was seen [Figure 1 b-m]. Based on imaging

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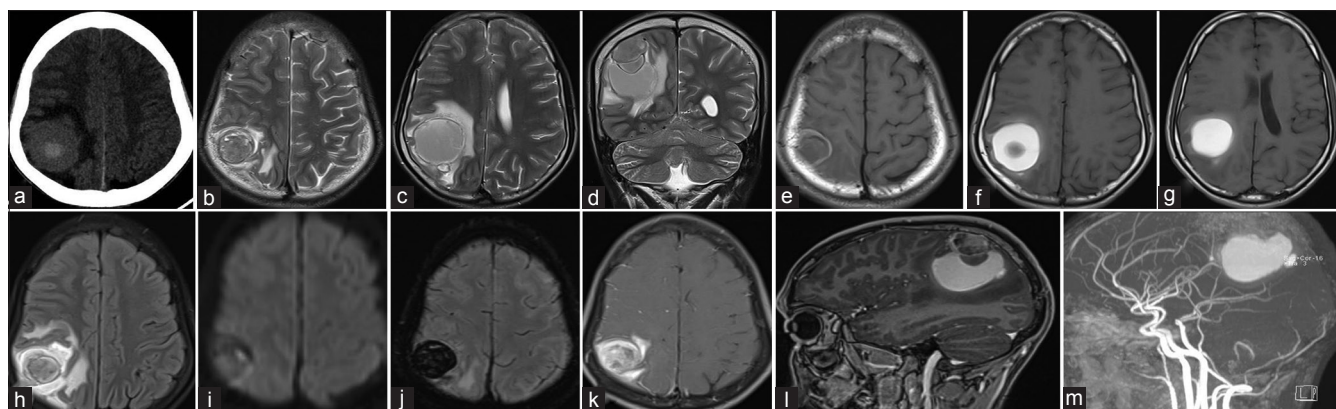
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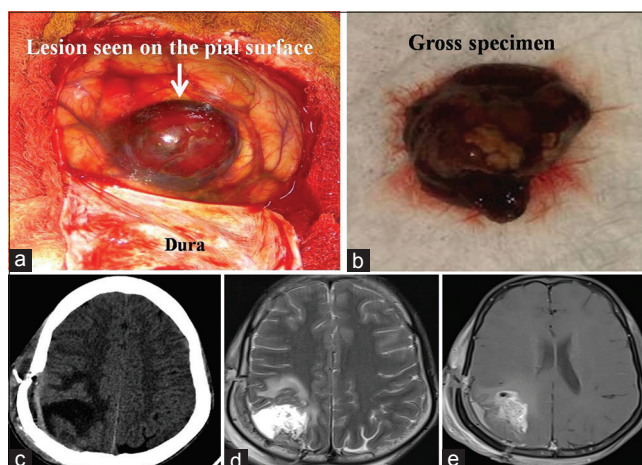


**Figure 1:** Computed tomography brain plain scan images (a) show cortical-based hyperdense lesion in the right parietal region with bleed. Magnetic resonance brain T2W axial (b and c) and coronal (d) images show right parietal cortical-based isointense lesion with bleed. T1W axial (e-g) shows lesion with bleed. Fluid-attenuated inversion recovery image (h) shows hyperintensity. Diffusion-weighted images image (i) shows peripheral restriction of the lesion and susceptibility-weighted images (j) images show intense susceptibility. Fat saturated T1W contrast axial (k) and sagittal (l) images show contrast enhancement of the lesion. Magnetic resonance angiography (m) shows normal flow signals

findings, we considered hemorrhagic mass lesions such as high-grade glioma or metastatic lesions as possibilities. He underwent a right parietal craniotomy and total excision of the lesion and evacuation of hematoma. Intraoperatively, hematoma was seen on the pia. The lesion was soft to firm, fleshy reddish dark brown, and vascular. Apart from the blood, there was no pigmentation of the meninges. There were no areas of pigmentation in the inner surface of the dura mater [Figure 2 a and b] Postoperative period was uneventful. Postoperative CT and MRI showed total excision of lesion with bleed [Figure 2 c-e].

Histopathology from paraffin blocks showed interesting features. Sections examined from the tumor showed cellular neoplasm composed of large cells with abundant eosinophilic cytoplasm, arranged in perivascular papillary pattern and in sheets. Tumor cells had coarse chromatin with brisk mitotic activity (8–10/10 hpf). At places, the tumor cells exhibited nuclear atypia. Focally, the tumor cells had intracytoplasmic brownish pigment along with hemosiderin-laden macrophages. Necrosis and thrombosed vessels were noted. The differential diagnoses considered based on these histological features were a high-grade glioma and a papillary meningioma.

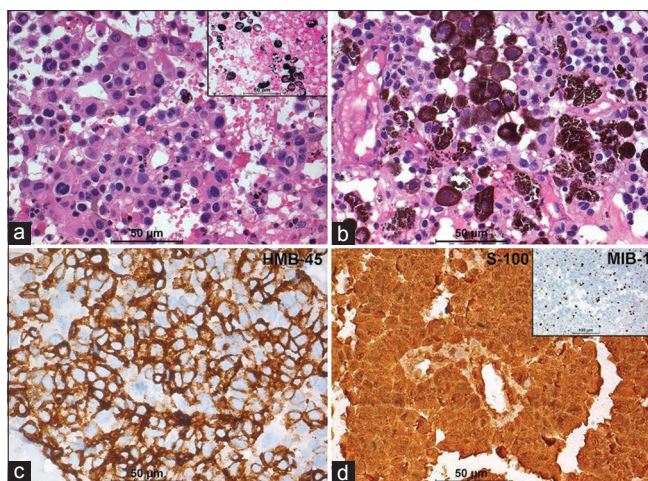
Immunohistochemistry for epithelial membrane antigen (EMA), glial fibrillary acidic protein (GFAP), IDH-1 (R132H), cytokeratin, CD34, chromogranin, and synaptophysin was negative and strongly positive for S-100 protein. INI-1 showed retained expression. MIB-1 labeling index was 15%–20%. In view of diffuse and strong S-100 immunohistochemistry (IHC), further IHC with human melanin black-45 (HMB-45) antibody was performed. The tumor showed strong HMB-45 immunopositivity and the final diagnosis of MM was offered [Figure 3 a-d]. BRAF mutations analysis could not be done in this patient as our laboratory was not equipped with the facilities for doing it.



**Figure 2:** Intraoperative picture (a) shows lesion on the pial surface and (b) shows gross specimen. Postoperative computed tomography brain plain (c), Magnetic resonance T2W and T1W axial (d and e) images show total evidence of lesion and evacuation of hematoma.

The patient underwent screening to look for the primary site for melanoma. A thorough search was made for a primary lesion in the other probable sites such as skin, mucus membrane, eyes, and lower gastrointestinal tract, which yielded negative results. CT scans of the thorax and abdomen yielded normal findings with no evidence of primary lesion. We confirmed that the intracranial lesion was a PMM. He was referred to oncologist for further treatment. Four months following surgery, he completed intensity-modulated radiotherapy 60 Gy in 30 fractions. He did not receive any chemotherapy. He again developed headache and vomiting immediately after completion of the radiation therapy. CT brain showed right parietooccipital bleed [Figure 4a and b]. MRI done showed a tentorial-based recurrent tumor in the right parietooccipital region. It was measuring 1.5 cm × 1.3 cm size. It was heterogenous intense in both T1 and T2W sequences with contrast enhancement. Gliotic area was seen in the previously operated cavity. Imaging confirmed a recurrent tumor





**Figure 3:** (a) Shows papillary arrangement of polygonal tumor cells with hyperchromatic nuclei and scant intracytoplasmic pigment in most of the areas. The melanin pigment is highlighted on Masson–Fontana stain (inset). (b) Shows a focus with intracytoplasmic brownish-black pigment within the macrophages and possibly few tumor cells. (c and d) Tumor cells are labeled by human melanin black-45 (c) and S-100 (d), with a high proliferative index (MIB-1, inset) (A: H and E, A, inset: Fontana–Masson, B: H and E; C: human melanin black-45, Immunoperoxidase; D: S-100, D, inset: MIB-1, immunoperoxidase. Magnification = scale bar)

remote from the previously operated site and away from the leptomeninges [Figure 4 c-h]. He underwent a right parietooccipital craniotomy and total excision of the tumor. Tumor was soft and suckable mixed with blood clots [Figure 4 i and j]. Falx and tentorium were seen and brain was lax at the end. The patient had a normal postoperative course without any complications. Postoperative CT confirmed total excision [Figure 4 k and l] and histopathology confirmed HMB-45 strongly positive recurrent melanoma. Five months following second surgery, the patient eventually succumbed to recurrence and expired.

## Discussion

PMM of the CNS is very unusual. It comprises 1% of all cases of melanoma, whereas primary intracranial MM comprises 0.7% of all primary tumors of the CNS with the incidence of 0.005 cases/100,000 population. Commonly, it is reported in age groups from 35 to 50 years.<sup>[2,6,8,9]</sup> The most common sites are; lobar (53.1%), posterior fossa (17.3%), and pineal region (13.6%), and with a male dominance. In children most often it is associated with neurocutaneous melanosis or giant congenital nevus.<sup>[1,2,6]</sup> PMM in the CNS includes in <3% of all childhood neoplasms.<sup>[4,10]</sup>

The melanocytes of the leptomeninges play a role in the origin of PMM in the CNS. Occasionally, the relatively few melanocytes dormant in the CNS can become neoplastic and are responsible for primary CNS melanomas.<sup>[11]</sup> It is also possible for small melanomas undetected before to present as brain metastases. In children, very often, it is associated with neurocutaneous melanosis. The recent theory explaining about primary melanomas is the overexpression of oncogenic NRAS in melanocytes during

embryonic development. NRAS mutations are the second most common mutations (20%) reported in MMs next to BRAF mutations (50%).<sup>[5]</sup> The somatic mutation in the NRAS oncogene in the melanocytes of the CNS is a risk factor to develop PMM in children.<sup>[1,6]</sup> It is often difficult to diagnose a primary CNS melanoma outright. Primary CNS melanoma is the diagnosis of exclusion from the more commonly seen metastatic disease in clinical practice.<sup>[5]</sup>

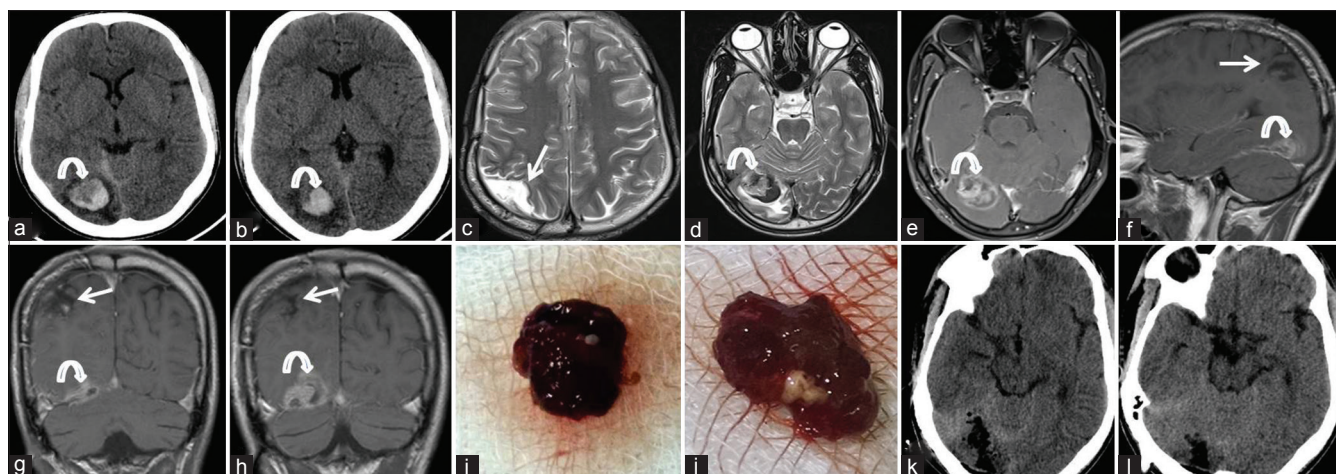
The common sites of PMM are the skin, eyes, oronasal mucosa, and anorectal junction. CNS metastases from primary melanoma occur in 10%–40% of patients. MM is the third most common tumour for CNS metastases, after breast and lung cancers. Headache, seizures, and neurological deficits are the presenting symptoms either in primary or metastatic tumors.<sup>[2,12]</sup>

The occurrence of primary MM in the brain in the absence of neurocutaneous melanosis is very uncommon.<sup>[2-5]</sup> Many of primary CNS melanomas were case reports collected from autopsy or associated with leptomeninges.<sup>[8,13,14]</sup> Few authors reported leptomeningeal melanomas in the literature.<sup>[7]</sup>

Melanomas are hyperdense in CT images with homogeneous contrast enhancement. Melanomas show unique imaging characters in MRI. They are hyperintense on T1-weighted images and hypointense on T2-weighted images due to paramagnetic effects of melanin. The radiological differentials are hemorrhage and metastatic tumor-like renal cell carcinoma which generally are associated with hemorrhage. These lesions show hyperperfusion on perfusion imaging and have an elevated choline and reduced N-acetylaspartate peak on MR spectroscopy.<sup>[5,6,15]</sup>

The commonly used immunohistochemical (IHC) markers for melanomas are HMB-45, Melan-A, S-100, and tyrosinase (TYR). The overall sensitivity is approximately 85%, that is, on par with other melanoma markers. Melan-A also belongs to gp100/pmel 17 glycoprotein family and show sensitivity to melanocytic cell lineage with sensitivity up to 85% in melanomas.<sup>[5,16]</sup>

The S-100 protein, a calcium-binding protein originally isolated from the brain, is a very useful IHC screening marker in the differential diagnosis of melanoma. More than 95% of primary cutaneous melanomas express S-100. It has less specificity for melanoma as it shows its wide-ranging immunoreactivity with neurons, reactive astrocytes, Langerhans cells, sweat glands, and Schwann cells.<sup>[17,18]</sup> Apart from melanoma, undifferentiated carcinomas and breast carcinoma show positivity to S-100. TYR, an enzyme with key role in melanin production, has been reported as a sensitive and specific marker. Its sensitivity is comparable with other markers in the range of 85%. Melanomas do not stain for EMA and this is used to differentiate from meningiomas or neurilemmoma and pigmented malignant schwannoma. Gliomas do not show



**Figure 4:** Repeat computed tomography plain (a and b) after radiation therapy shows tumor with bleed. Magnetic resonance T2W axial images (c and d) show isodense tumor with bleed in the right occipital region, axial (e), sagittal (f), and coronal contrast images (g and h) show recurrent contrast-enhancing tentorium-based occipital tumor (large arrows) and small arrows show previous operated cavity. Intraoperative pictures (i and j) show the gross specimen. Postoperative computed tomography plain (k and l) shows complete excision of the tumor

reactivity with both HMB-45 and Melan-A, although GFAP may be positive in few cases of melanomas.<sup>[6,16]</sup>

Microphthalmia transcription factor (MITF) is reported as having 100% sensitivity for metastatic melanoma.<sup>[19]</sup> MITF is a relatively specific marker for melanoma and related tumors. It is not as specific or as sensitive as TYR. Metastatic melanomas stain positively to vimentin and S-100. MITF is important for the survival of melanocytes and regulates several melanocyte genes. Its usefulness lies in positivity showing by some melanomas, for which other markers were negative. Few authors reported almost 50% of the S-100, HMB-45 negative melanomas, and a few TYR- and Melan A-negative melanomas were MITF-positive. These authors suggested MITF is a useful additional IHC marker for metastatic melanoma. However, it is noteworthy to mention that desmoplastic variant does not show positivity even to MITF. NKI/C3 proved to have better sensitivity than S-100 protein, in staining HMB-45 negative melanomas. However, its specificity is inferior to HMB-45 and superior to S-100. Few authors suggested that few melanomas may lose HMB-45 positivity in the process of becoming metastatic from the primary.

There are no standard guidelines available for the management of the primary CNS melanomas. There are no randomized trials in the treatment of these tumors. Surgical excision of the tumor is the first line of management. Radiotherapy and chemotherapy play vital role, nevertheless, it has been considered that melanomas often are radioresistant or chemoresistant tumors.<sup>[5-7]</sup> Chemotherapeutic agents that have been tried along with radiation therapy include BRAF inhibitors, dacarbazine together with 3-nitrosourea hydrochloride, and vincristine with OK-432 show good results in both primary and metastatic tumor. Intraventricular chemotherapy and intrathecal recombinant interleukin-2 are also tried. Few authors suggested ipilimumab and vemurafenib in primary CNS MM.

The prognosis of primary intracranial MM is better than that of metastatic MM, with full resection, despite the aggressive multimodal management, the reported survival in secondary intracranial MM is 3–6 months compared to that of patients with the diagnosis of primary intracranial MM which is around 27 months.<sup>[6]</sup> In case of the pediatric population, the primary melanoma of the CNS is of poor prognosis in contrast to adult population and is associated with a meager survival of 8 months from the initial presentation. Our case highlights that even the whole-brain radiation therapy could not prevent from recurrence and the disease progression and finally leads to mortality. Similar observations were made by authors where the patient expired after 10 weeks following surgical excision and whole brain radiation therapy.

The present case is unique in many ways. There was no evidence of hyperpigmented patches, nevi either cutaneous or on mucosa in this case. It was not associated with syndrome like neurocutaneous melanosis, and there was no evidence of leptomeningeal melanosis. Primary MM presenting like intraaxial solitary brain tumor with similar histological features sharing with anaplastic ependymoma or papillary meningioma are not yet reported in the pediatric population. Recurrence of tumor immediately after radiation therapy and finally succumbing to it within 6 months of total excision of recurrence showed aggressiveness.

## Conclusions

The present case illustrates the challenge to diagnose the primary CNS melanoma in the absence of any markers of cutaneous melanosis in pediatric age. A high index of clinical suspicion along with precise pathology reporting by applying melanoma-specific markers is the key in diagnosing these extremely uncommon tumors, especially in pediatric age group. The suggested treatment option is



total surgical excision followed by postoperative adjuvant therapy with radiation and chemotherapy. The rapid uncontrolled progression of the disease in spite of complete excision and whole-brain radiation therapy, in the present case, emphasizes further evaluation of the role of BRAF inhibitors, immunotherapy, and intrathecal chemotherapy in the management of melanoma.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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#### Conflicts of interest

There are no conflicts of interest.

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