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CASE REPORT

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Primary central nervous system amelanotic melanoma in a Hispanic male: Case report

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Summary

Background: Primary melanotic neoplasms of the central nervous system (CNS) are uncommon; amelanotic melanomas in this region are extremely rare. Very few cases of amelanotic variation of primary melanoma in the CNS were reported on. General guidelines or recommendations to establish this diagnosis do not exist.

Case Report: A sixty-year-old male Hispanic patient presented with a 7-day history of numbness and dizziness. Initial laboratory work-up and physical examination were inconclusive. Cerebral radiological imaging showed a left frontal lesion. Further work-up after clinical deterioration revealed an increase in the lesion size consistent with hemorrhage and changes in T1WI. Biopsy and immunochemistry demonstrated the presence of amelanotic melanoma in the CNS without evidence of another primary lesion.

Conclusions: Primary amelanotic melanoma of the CNS represents a challenge, clinically and diagnostically. Magnetic resonance imaging can be helpful in early stages. Final diagnosis is established with immunohistochemical testing. Physicians should be aware of the existence of this rare manifestation and difficulties faced while building this diagnosis.

MeSH Keywords: Magnetic Resonance Angiography • Melanoma, Amelanotic • Tumor Markers, Biological

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Background

Melanoma was estimated to cause 12,650 deaths in 2013 and was diagnosed in 76,690 patients [1]. Malignant melanoma has a high potential for growth and metastasis, and is the cause of 75% of skin cancer deaths [2]. In particular patients with metastases to the brain have a median survival of 4.1 months from time of diagnosis [3] and account for 20–54% of cases of death due to melanoma [4]. Primary lesions on the head and neck have been associated with metastasis to the brain as well as decreased survival time [5]. Because of a high rate of metastatic melanomas found in the brain and associated poor prognosis, further research is warranted.

Amelanotic melanoma represents a variant that has a reported incidence of 2–8% of diagnosed melanomas [6]. The definitions of amelanotic melanoma may vary, but they all include a characteristic feature, i.e. absence or minimal amounts of melanin pigment as a notable trait. This lack of melanin can lead to the disease being misdiagnosed and often requires the use of stains such as S100 protein and HMB45 to aid in proper identification [7]. Indeed, previous cases found in the cervix and rectum, were initially suspected to be non-epithelial tumors or carcinoma before immunostaining provided the diagnosis of primary amelanotic melanoma [8–10]. Amelanotic melanoma constitutes a challenge for physicians as concerns its detection and treatment before metastasis occurs and symptoms appear in patients.

Table 1. Initial laboratory work-up upon admission.

Laboratory work up	
White blood cell count	10.54×10^3 uL
Segments	78.7%
Eosinophiles	0.5%
Lymphocytes	12.7%
Monocytes	7.4%
Hemoglobin	16.3 g/dL
Hematocrit	44.8%
Platelet count	247×10^3 uL
Sodium	143 mmol/L
Potassium	4.3 mmol/L
Chloride	99 mmol/L
CO2	22 mmol/L
Serum glucose	127 mg/dL
BUN	23 mg/dL
Creatinine	1.29 mg/dL
Calcium	10.2 mmol/L
Albumin	4.4 g/dL
Protein	7.8 g/dL
AST	29 I.U./L
ALT	45 I.U./L
Alk. phosphatase	85 I.U./L

Here we present an unusual case of amelanotic melanoma found in the brain, which was diagnosed within only a few days despite all the difficulties with establishing this diagnosis, described in the literature.

Case Report

A sixty-year-old Hispanic male patient with a history of hypertension, diabetes mellitus type II, without a significant surgical history presented to the ED with progressive dizziness, ataxia, numbness and tingling of his fingers bilaterally, nausea and vomiting over the last 7 days. Family history was significant for myocardial infarct in his mother. He denied the use of alcohol, illegal drugs or smoking. He lived with his wife and was in his usual state of health until those symptoms began. Vital signs showed normal temperature (36.6°C), heart rate of 71 beats per minute, and hypertension of 161/75 mmHg.

Physical examination was remarkable for intermittent decreased sensitivity on his both upper extremities, symmetrically. The rest of the examination, including a neurological test, was unremarkable. Initial laboratory work-up is shown in Table 1.

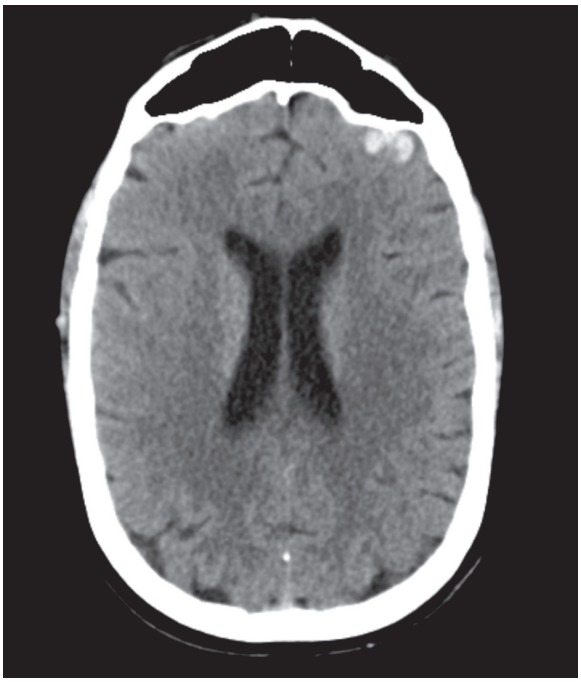

Figure 1. A 15×9 mm area of hemorrhage with surrounding vasogenic edema in the left anterior middle frontal gyrus. No midline shift, hydrocephalus, mass lesion, or cerebral herniation.

Table 2. Cerebrospinal fluid analysis.

CSF	
Color	Yellow
Appearance	Hazy
White blood cell count	8×10^3 uL
Red blood cell count	9×10^3 uL
Protein	36 mg/dL
Glucose	58 mg/dL

Computed tomography (CT) of the brain showed intraparenchymal hemorrhage in the anterior aspect of the left frontal lobe (Figure 1). Magnetic Resonance Imaging (MRI) of the head was indicative of an acute generalized vasculopathic process involving the supra- and infratentorial compartments, resulting in multifocal petechial cortical hemorrhages and disruption of the brain-blood barrier with secondary contrast leakage. The angiographic sequences demonstrated multifocal alternating luminal narrowing and dilation that involved predominantly the bilateral ACAs. The aforementioned findings were nonspecific. With imaging, the differential diagnosis at that point included reversible cerebral vasoconstriction syndrome, intracranial vasculitis and cerebral vasculopathy versus other less frequent pathologies like intravascular lymphoma and hemorrhagic encephalitis.

The neurology consultation team was involved and cerebrospinal fluid was obtained (Table 2), which was unremarkable. The results of further laboratory work-up as

Table 3. Further laboratory work-up and cultures.

ANA	Negative
Anti-DNA DS	Negative
Culture CSF	Negative
Culture fungal	Negative
Culture anaerobic	Negative
Parasite negative	Negative
Crypto antigen in CSF	Negative
VDRL CSF	Negative
HBs antigen	Negative
HB core antigen	Negative
Hepatitis A IgM	Negative
Hepatitis C	Negative
Cytomegalovirus PCR	Negative
ANCA IgG	Negative
Herpes simplex PCR CSF	Not detected
HSV IgM and IgG	Negative

well as serum and CSF cultures are displayed in Table 3, and were unremarkable as well. Further radiological studies including CT of the chest, abdomen and pelvis did not yield any explanatory findings. MRI of the spinal regions did not show any lesions.

Meanwhile, the patient was placed on supportive and antiepileptic therapy. On the 5th day of hospitalization, the medical staff noted a decreased level of consciousness and a Glasgow Coma Scale (GSC) score of 9. He was transferred to the Intensive Care Unit and another CT of the brain was performed which showed a remarkable progress of the parenchymal hemorrhage in the left frontal lobe with prominent perilesional edema, regional sulcal effacement and 11 mm of left-to-right subfalcine herniation. After stabilizing the patient, a follow-up MRI of the brain was performed which showed an increase in number of petechial cortical hemorrhages noted within bilateral frontal cerebral convexities, left occipital lobe, cerebellum, and vermis (Figure 2). Differential diagnoses were re-discussed at that point and the neurology consultation service assumed a demyelinating process. However, since those symptoms were acute we involved the neurosurgery team, which decided to obtain a biopsy from the left frontal lobe. Surprisingly the biopsy demonstrated features of melanoma. The discolored tumor cells were positively tested for the markers S-100 and HMB-45 in the immunohistochemistry; anti-Melan-A was negative. The MIB-1 proliferation index was >10%. The diagnosis of amelanotic melanoma was established within a few days after the initial presentation.

Despite having the patient seen by several physicians over that period of time, no dermatological lesion was noted. Another extensive physical examination was performed and no suspected lesions of the skin, mucosa or eyes were seen. Further laboratory/genetic testing for BRAF V600 mutation, which is helpful in determining the type of treatment, was positive. The results were discussed with the patient and his family. After 7 days of treatment he was discharged home and follow-up was scheduled in the

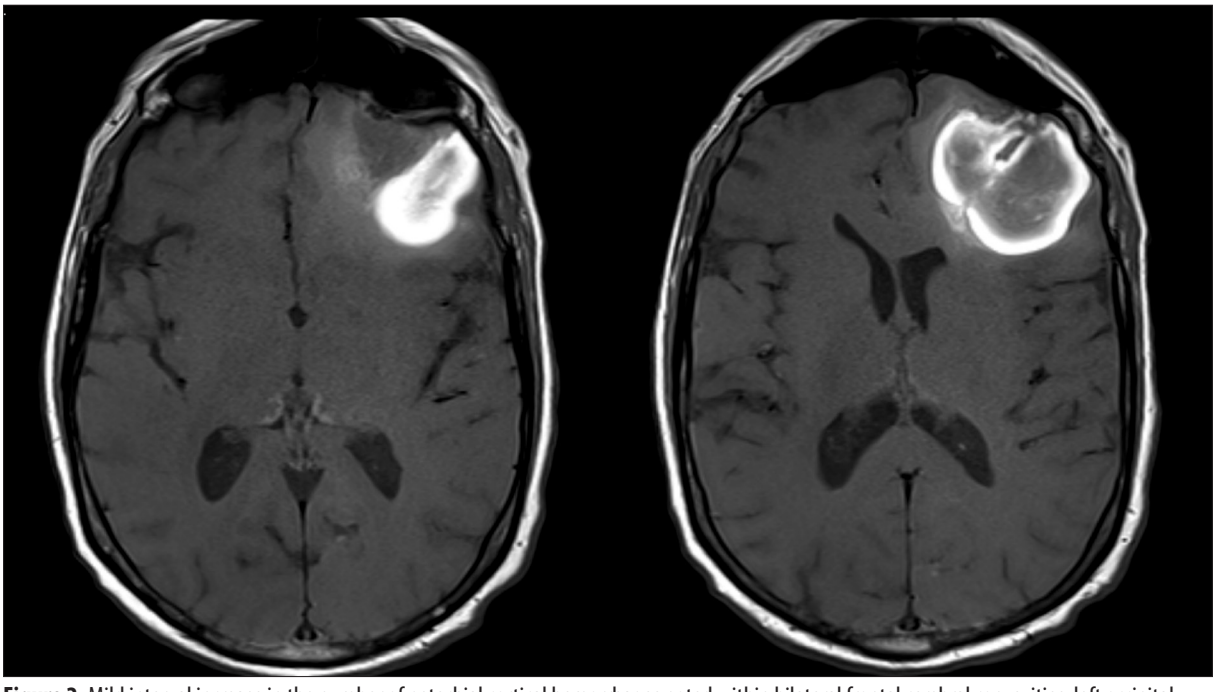

Figure 2. Mild interval increase in the number of petechial cortical hemorrhages noted within bilateral frontal cerebral convexities, left occipital lobe, cerebellum, and vermis. A subacute left frontal parenchymal hemorrhage of 4.9 cm, with associated edema; mass effect resulting in 9-mm rightward midline shift and small subfalcine herniation.

hemato-oncology outpatient clinic to determine whether he can be started on Vemurafenib and dabrafenib.

Discussion

Malignant melanoma is well known for a high rate of cutaneous metastases. Melanomas commonly present with pigmented lesions containing melanin granules, which allows them to be visually detected by clinicians.

Primary isolated intracranial amelanotic melanomas, with their atypical features, remain a challenge to diagnose before clinical symptoms present. A set of criteria to identify a primary CNS melanoma was established in 1976 by Hayward and was modified over the last decade. According to that set, a primary CNS melanoma can be diagnosed after a positive cerebral biopsy, even if extensive dermatological, mucosal and ophthalmological examinations were inconclusive [11].

Intracranial malignant melanomas demonstrate a moderate to high intensity in T1WI and a low intensity in T2WI, while amelanotic melanomas demonstrate a low intensity in T1WI and a high intensity in T2WI [12,13]. Indeed, in our patient, metastatic amelanotic melanoma was not suspected until clinical progress occurred and changes were noted in the imaging modalities, which led to the decision to perform a biopsy [14].

Intratumor hemorrhages may easily develop from melanotic melanomas. However, when this happens, the diagnosis is limited to amelanotic melanoma. Furthermore, a primary cerebral amelanotic melanoma or metastatic amelanotic melanoma of unknown origin represents a clinical challenge for the internists, neurosurgeons and radiologists. Melanotic or amelanotic melanoma cannot be diagnosed based on MR images. There are almost no variations in findings on intracranial melanomas. Therefore, MR images are not used to differentiate between melanotic and amelanotic melanomas.

The diagnosis follows from a combination of clinical suspicion, felicitous radiological presentation and pathological findings. However, immunochemistry should be considered mandatory to confirm the diagnosis [15]. The presence of S-100 is typical for melanoma; HMB-45 is a standard marker of melanoma, which was positive in our case [16]. This finding in combination with negative results for anti-melan-A confirmed the diagnosis of amelanotic melanoma in our case.

Conclusions

As shown in our rare case, primary amelanotic melanoma of the CNS is a diagnosis difficult to establish and presents a diversity of clinical findings. The clinical suspicion only is insufficient in this scenario. However, once malignancy is suspected a combined set of criteria is needed to establish this difficult diagnosis. Radiologic imaging, especially MRI of the brain, is essential and helpful. The final diagnosis is delivered with an additional set of specific tumor markers. Definite treatment is surgical, but there were a few cases of successful use of chemotherapeutic agents.

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