

## CASE REPORT

# Primary versus Secondary Central Nervous System Melanoma: a Diagnostic Dilemma and Report of a Case

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## Abstract

**Introduction:** Malignant melanoma is a cancer of melanocytic origin, typically cutaneous. Despite recent advances, the prognosis is poor. Brain metastases occur in approximately 7-16% of cases and leptomeningeal metastases in 5-7%. Primary central nervous system (CNS) melanoma is rare, accounting for 1% of all melanoma cases and 0.07% of brain tumors. **Methods:** A 65-year old man presented with haemorrhagic venous infarction of the left temporal lobe, leading to reversible motor aphasia and right-sided hemiparesis. Brain magnetic resonance imaging also revealed peculiar supratentorial cerebral and meningeal lesions suggesting neoplasia or vasculitis. Ancillary tests were unremarkable, a brain biopsy was proposed, but the patient declined. After 1.5 years symptoms recurred and imaging studies found progression of lesions, with necrosis and surrounding vasogenic oedema. The patient finally agreed to a brain biopsy for conclusive diagnosis. **Results:** Histopathological and immunohistochemical assessment was consistent with malignant pigmented melanoma. There were no suspicious primary lesions, but the patient recounted having had a thoracic skin lump excised some years prior, allegedly benign, yet unavailable for second opinion. **Conclusion:** In suspicious CNS presentations, histopathological reevaluation of previously excised skin lesions is advised, especially if brain biopsy cannot be performed. Albeit rare, primary CNS melanoma should also be considered.

**Keywords:** melanoma, cerebral metastases, second opinion.

## Rezumat

**Introducere:** Melanomul malign este un cancer cu origine melanocitară, cu dezvoltare tipic cutanată. Prognosticul este nefavorabil în pofida progreselor recente. Metastazele cerebrale apar în aproximativ 7-16% din cazuri, iar metastazele leptomeningeale în 5-7%. Melanomul primar al sistemului nervos central este rar, reprezentând 1% dintre toate cazurile de melanom și 0,07% dintre tumorile cerebrale. **Metode:** Prezentăm cazul unui bărbat în

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vârsta de 65 de ani cu infarct venos hemoragic la nivelul lobului temporal stâng responsabil de afazie motorie și hemipareză dreaptă. Rezonanța magnetică cerebrală a evidențiat de asemenea leziuni supratentoriale cerebrale și meningeale suspecte, cu posibil substrat neoplazic sau vasculitic. Bilanțul investigațional nu a fost concludent, s-a propus biopsia cerebrală, însă pacientul a refuzat. După 1,5 ani de la simptomatologia inițială, simptomele au reapărut, iar imagieria cerebrală a relevat progresia leziunilor, cu necroză și edem vasogenic înconjurător. În cele din urmă, pacientul a consimțit la efectuarea biopsiei cerebrale pentru diagnostic de certitudine. **Rezultate:** Evaluarea histopatologică și imunohistochimică a fost compatibilă cu melanom malign pigmentat. Nu s-au depistat leziuni primare suspecte, însă pacientul și-a amintit faptul că în urmă cu câțiva ani i s-a excizat o formațiune toracică, aparent benignă, însă indisponibilă pentru second opinion. **Concluzii:** În cazul prezentărilor suspecte ale sistemului nervos central, reevaluarea histopatologică a leziunilor cutanate excizate anterior este recomandabilă, mai ales atunci când nu se poate practica biopsia cerebrală. Melanomul primar al sistemului nervos central, deși este rar, reprezintă un diagnostic de avut în vedere.

**Cuvinte-cheie:** melanom, metastaze cerebrale, second opinion.

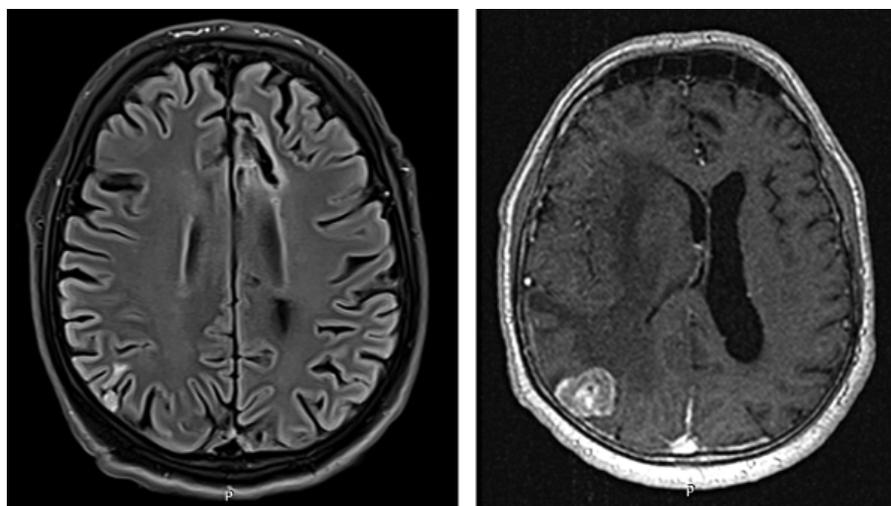
## INTRODUCTION

Melanoma is the third most frequent cause of brain metastases, after lung and breast cancer, accounting for approximately 6-11% of all metastatic brain lesions<sup>1,2</sup>. Apart from cutaneous melanoma, which is the commonest subtype, melanoma may also arise from other sites containing melanocytes such as the glabrous skin of the palms, soles and nail beds (i.e. acral melanoma), the mucosal epithelium lining the respiratory, alimentary and genitourinary tracts, the conjunctival epithelium, the uveal tract and the leptomeninges<sup>3</sup>. Primary central nervous system (CNS) melanoma is rare, comprising 1% of all cases of melanoma and 0.07% of brain tumours<sup>4</sup>. Herein we report the case of a patient with melanoma of uncertain origin, cutaneous in all likelihood, and brain metastases, with a view to raising awareness of the matter and delineating the particularities

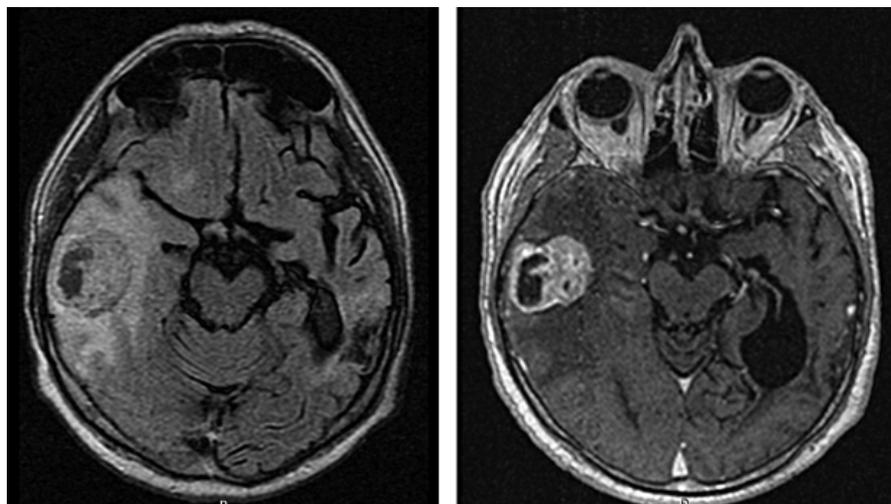
of timely diagnosis and treatment with irrefutable impact upon prognosis.

## CASE REPORT

A 65-year old Caucasian male, hypertensive, diabetic, with long-term anticoagulant and antiplatelet therapy, and a history of myocardial infarction initially presented with a hemorrhagic venous infarction of the left temporal lobe responsible for sudden motor aphasia and right-sided hemiparesis, which he recovered completely over the next year. A follow-up brain magnetic resonance imaging (MRI) performed six months later revealed an asymptomatic hemorrhagic venous infarction in the territory of the left vein of Labbe, as well as peculiar intra-axial and meningeal lesions of the right hemisphere (Figure 1, left). At the time he was referred to our Department and underwent a comprehensi-



**Figure 1.** Brain MRI. Axial fluid attenuation inversion recovery (FLAIR)-weighted image showing a right parietal mass of probable meningeal origin (left) and axial T1-weighted image showing the same mass of larger size, with surrounding vasogenic oedema, seven months later (right).



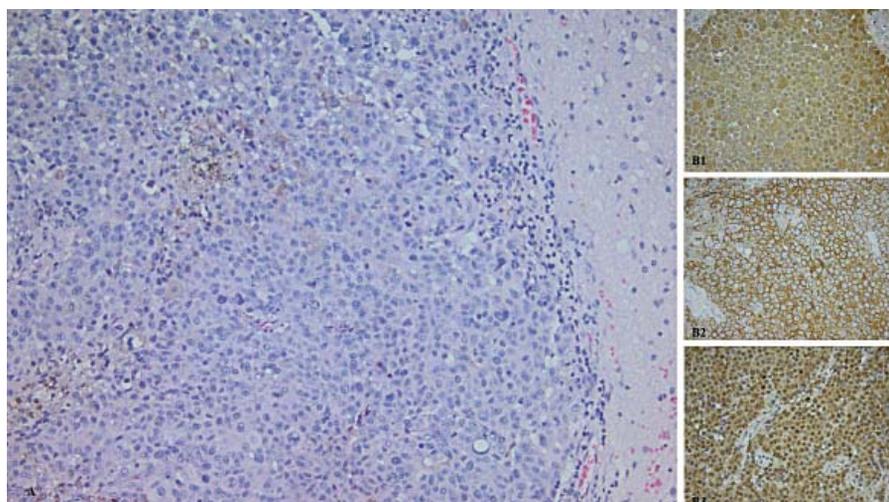
**Figure 2.** Brain MRI. Axial FLAIR-weighted image (left) and T1-weighted image (right) showing a right temporal contrast-enhancing lesion with an inner necrotic area and surrounding vasogenic oedema.

ve workup covering a potential neoplastic or vasculitic ground, comprising extensive blood testing, lumbar puncture with cerebrospinal fluid analysis, including oligoclonal bands, immunoglobulin G index and lymphocyte immunophenotyping, all of which were unremarkable. A brain biopsy was discussed, but the patient declined. He was readmitted after five months for left-sided hemiparesis 3/5 BMRC and motor aphasia. Brain MRI showed progression of lesions with expansion of a right parietal mass of probable meningeal origin described on previous examination (Figure 1, right) and a novel right temporal lesion with an inner necrotic area and surrounding vasogenic oedema (Figure 2). There was complete neurological remission upon treatment with dexamethasone. The patient finally agreed to undergo neurosurgical treatment and one month later tumour debulking and brain biopsy were performed for histological and immunohistochemical assessment, which were consistent with cerebral metastasis from malignant pigmented melanoma (Figure 3). There were no clinically suspicious primary lesions, however the patient recalled having had a thoracic lump excised some years prior, allegedly benign, but unavailable for second opinion.

## DISCUSSION

This case is a starting point for revising general important aspects concerning melanoma, a major health issue whose overall prognosis is grounded on timely diagnosis and treatment. Although there are no randomized trials to establish the efficacy of screening for melanoma on mortality reduction, screening is sensible for persons considered at high risk of developing

melanoma, i.e., fair-skinned, carrying a history of sun exposure, a family or personal history of skin cancer, an increased number of nevi and atypical nevi, an immunocompromising condition<sup>5</sup>. Screening involves a full-body examination performed yearly by a trained specialist, education about risk factors and monthly self-examination. The *US Preventive Services Task Force* (USPSTF) hold that there is insufficient evidence to assess the benefits and harms of counseling adults about skin self-examination, but recommend that counseling be provided for children, parents of children and adults with fair skin about minimizing exposure to ultraviolet radiation<sup>5</sup>. The ABCDE criteria for the assessment of pigmented cutaneous lesions are instrumental in early detection of cutaneous melanoma. The acronym stands for asymmetry, border irregularities, colour variegation, diameter equal to and over 6 mm and evolution<sup>6</sup>. All suspicious pigmented lesions should be further examined dermoscopically<sup>7</sup>. The definitive diagnosis of melanoma is histopathologic, with supporting immunohistochemical testing. Aside from cutaneous melanoma, which is the most common type, there are also other unusual types of melanoma such as acral, mucosal, conjunctival, uveal and leptomeningeal melanoma<sup>3</sup>, that tend to be diagnosed at a more advanced stage and therefore bear a worse prognosis<sup>8</sup>. Melanoma has a strong propensity for brain metastases<sup>2</sup>. Cerebral haemorrhagic masses should prompt considering the existence of a melanoma with subsequent thorough clinical screening. In the setting of melanoma and cerebral lesions, the latter are more likely brain metastases, yet a primary CNS melanoma, albeit less frequent, should also be entertained. As regards the therapeutic management of melanoma patients with



**Figure 3.** Histopathological specimen hematoxylin and eosin stained, 200 times enhanced, showing malignant melanocytic proliferation (A) and immunohistochemical stains 400 times enhanced confirming the melanocytic origin through S100 positivity (B1), HMB45 positivity (B2) and MITF positivity (B3).

brain metastases, a multidisciplinary approach is warranted. Important factors to consider in treatment selection are tumour-related, such as number, size, location of brain metastases, B-Raf (BRAF) mutation status of the melanoma, as well as patient-related, including age, overall performance status, other comorbidities and the extent of systemic metastatic disease. Surgical resection is generally preferred in patients with a good performance status (i.e. Karnofsky performance status over 70%), with solitary or few brain metastases located in noneloquent areas or to relieve symptoms from larger lesions (greater than 3 cm), and potentially life-threatening ones<sup>9</sup>. Stereotactic radiosurgery (SRS) is employed for multiple small lesions (under 3 cm in diameter)<sup>10</sup> or lesions that are not surgically accessible. The total tumour volume appears to be a better prognostic of outcome, including overall survival, than the number of metastases<sup>11</sup>. The advent of systemic therapy comprising immunotherapy and targeted therapy has significantly advanced the treatment of metastatic melanoma. The combination of ipilimumab and nivolumab has proven more effective in improving overall survival than either agent in monotherapy as regards advanced melanoma<sup>12</sup> and brain metastases in melanoma specifically<sup>13</sup>. Furthermore, associating immunotherapy with surgical treatment or radiosurgery resulted in longer median overall survival<sup>14</sup>. Targeted agents are inhibitors of protein kinases involved in the mitogen-activated protein kinase (MAPK) pathway, which is pivotal in the pathogenesis of melanoma. Therefore, BRAF inhibitors such as dabrafenib, vemurafenib or MEK inhibitors such as trametinib have shown benefit in overall survival were mutations in BRAF V600E

and BRAF V600 respectively were concerned<sup>15</sup>. There is still concern about devising proper protocols combining systemic therapy agents and immunotherapy with local surgery and radiosurgery, but the outlook is encouragingly promising. Nevertheless, a prompt diagnostic is a key-element for a beneficial outcome. In our patient there are no follow-up data over 2.5 years from the initial neurological manifestations, yet the prolonged survival surpassing the reported overall average of four months<sup>16-18</sup> is particular.

## CONCLUSION

- Unusual sites of origin for melanoma are the mucosal epithelium lining the respiratory, digestive and genitourinary tracts, the conjunctival epithelium, the uveal tract and the leptomeninges
- Prompt histopathologic reevaluation of previously excised skin lesions should be considered in people with suspicious CNS presentations, especially if CNS biopsy cannot be performed.

**Disclosure:** This case report was first presented as ePoster at the 4<sup>th</sup> Congress of the European Academy of Neurology in June 2018.

### Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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