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CASE REPORT

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Imaging findings in carcinomatous encephalitis secondary to malignant melanoma

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Abstract

Background The case of disseminated cancer cell spreading throughout the brain is called "miliary metastases" or "carcinomatous encephalitis", a very rare and critical condition (primarily associated with lung and breast cancer) in which there are multiple plaque with a perivascular distribution, made of punctate lesions spread in all the brain. To our knowledge this represents the fourth case of melanotic miliary brain metastases described in the literature, also associated with melanin content of the lesions that is already evident on unenhanced T1-weighted images.

Case presentation A 75-year-old patient with history of metastatic cutaneous melanoma (BRAF V600E mutate, PD-L1 negative) in treatment with dabrafenib and trametinib after 9 years from the diagnosis developed severe cognitive-motor slowing. Contrast-enhanced brain MRI showed miliary enhancing intra-axial brain lesions involving supra- and sub-tentorial regions and also the perivascular spaces, characterized by a bright appearance on unenhanced T1-weighted images without signal hypointensity in T2*-weighted images, as for melanotic pattern. Thus, the radiological diagnosis of "carcinomatous encephalitis" was made. Neurological examination showed an alert and cooperative subject with increased reaction time in verbal and motor responses. No ocular motility disturbances were found, and there were no motor or sensory deficits in the four limbs. The finger-to-nose test was normal, and no coordination deficit was found bilaterally. Blood tests and body temperature demonstrated no signs of ongoing infection. Electroencephalography showed slow and punctate abnormalities in bilateral fronto-temporal regions, with left prevalence. Corticosteroid therapy was started during hospitalization, improving the clinical picture. The patient was then discharged after 4 days in good clinical conditions with the indication to start second-line treatment with ipilimumab and nivolumab and to perform a whole-brain irradiation.

Conclusions Brain MRI plays a crucial role for the non-invasive diagnosis of carcinomatous encephalitis and for the differential diagnosis with other pathologies. Awareness of the existence of this disorder even in patients with melanoma is necessary to avoid diagnostic delays. Miliary brain metastases should be suspected in all melanoma patients with new neurological findings and contrast-enhanced MRI should be performed to assess the real burden of the disease.

Keywords Miliary, Brain, Metastases, Melanoma, Magnetic resonance imaging

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Background

Malignant cutaneous melanoma is the most common subtype of malignant melanoma, a neoplasm that arises from melanocytes, with an incidence of 18.3 per 100,000 people per year, which is increasing in the last decade [1].

The case of disseminated cancer cell spreading throughout the brain is called "miliary metastases" or "carcinomatous encephalitis" (CE), a very rare condition in which there are multiple plaque with a perivascular distribution [2], made of punctate lesions spread in all the brain.

We present the fourth case of melanotic miliary brain metastases described in the literature, also associated with melanin content of the lesions that is already evident on unenhanced T1-weighted images [3–5].

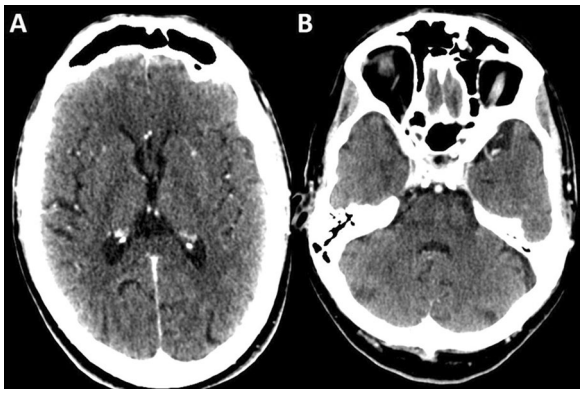

Fig. 1 Contrast-enhanced head computed tomography scan. **A** Supra-tentorial region shows a few millimeter diameter areas of enhancement at the putamen level. **B** Sub-tentorial region shows no clear areas of enhancement in the cerebellum

Case presentation

A 75-year-old patient being treated for metastatic melanoma was urgently admitted to the Oncology Department for incipient worsening of general clinical condition, with cognitive-motor slowing.

The patient's oncologic history started in November 2013 with the removal of cutaneous melanoma of the left shoulder histologically classified as superficial spreading melanoma with vertical growth, infiltrating the reticular dermis (Clark's level of IV; Breslow's depth of 0.82 mm). Cutaneous margin enlargement and sentinel lymph node were negative for disease localization. In august 2014, he removed an additional skin melanoma at the level of the left scapula histologically classified as melanoma in situ (Breslow's depth of 0.3 mm). In subsequent years, the patient underwent further excisions of numerous basal cell and spinocellular carcinomas for which he continued regular dermatologic and radiologic follow-ups with no evidence of recurrence. Whole-body computed tomography (WB-CT) performed in March 2022, showed the appearance of multiple metastatic lesions, at the level of the brain, lungs, liver, right adrenal gland, spleen, peritoneum, spine, and in the subcutaneous fatty tissue. The subsequent biopsy of one of the liver lesions and one of the subcutaneous lesions confirmed metastatic localization of melanoma (BRAF V600E mutate, PD-L1 negative). Magnetic resonance imaging (MRI) of the brain documented at least 7 metastases located in the supratentorial cortico-subcortical site and at the level of the basal ganglia (maximum diameter of 6 mm). At the end of March 2022, the patient then started systemic therapy with dabrafenib and trametinib with a good response at the WB-CT performed in May 2022.

In September 2022, the subsequent WB-CT (Siemens Somatom Definition AS, Siemens Healthcare, Erlangen, Germany, after intravenous administration of 120 ml of Omnipaque 350 mgI/ml, Ioexolo, GE Healthcare, Chicago, Illinois, United States of America) documented the appearance of highly vascularized lesions in the brain, suggestive of metastatic lesions (Fig. 1). After 2 weeks (October 2022), the patient complained of severe cognitive-motor slowing and therefore underwent a contrast-enhanced brain MRI (1.5 T Magnetom Symphony, Siemens, Erlangen, Germany, before and after intravenous administration of 10 ml of dotagraf 0.5 mmol/ml, gadoteric acid, Bayer, Leverkusen, Germany) (Fig. 2). The examination showed miliary enhancing intra-axial brain lesions involving supra- and sub-tentorial regions and also the perivascular spaces (PVS), characterized by a bright appearance on unenhanced T1-weighted images without signal hypointensity in T2*-weighted images, as for melanotic pattern. Clear involvement of the meninges had not been identified. Thus, the radiological diagnosis of "carcinomatous encephalitis" was made and the patient was urgently admitted to the Oncology Department. A neurological examination was performed, which showed an alert and cooperative subject with increased reaction time in verbal and motor responses. No ocular motility disturbances were found, and there were no motor or sensory deficits in the four limbs. The finger-to-nose test was normal, and no coordination deficit was found bilaterally. Body temperature and blood tests demonstrated no signs of ongoing infection (body temperature: 35.7 °C; white blood cell count: 5.52×10^3/μl; procalcitonin: 0.11 ng/ml). Electroencephalography showed slow and punctate abnormalities in bilateral fronto-temporal regions, with left prevalence. Corticosteroid therapy (dexamethasone 4 mg) was started during hospitalization, improving the clinical picture. The patient was then discharged after 4 days in good clinical conditions with the indication to start second-line treatment with

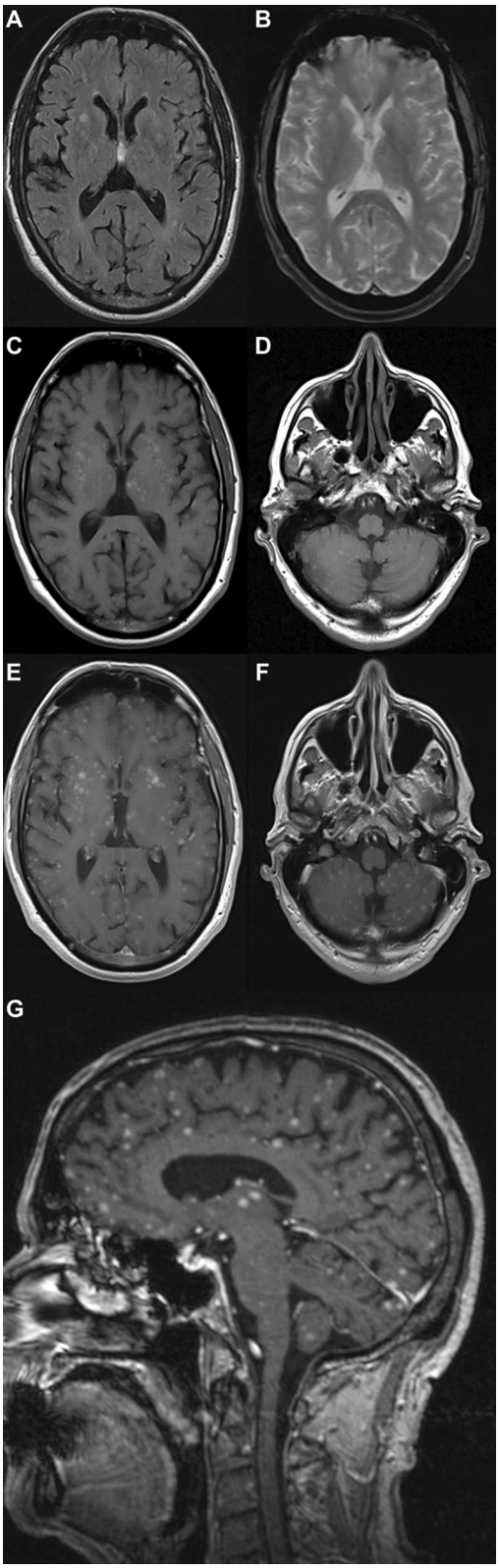

Fig. 2 Contrast-enhanced brain magnetic resonance imaging show miliary brain metastases (also called "carcinomatous encephalitis") from malignant melanoma. **A** Fluid-attenuated inversion recovery image shows the presence of some hyperintense signal areas, most evident at the level of the basal ganglia. **B** Fast low-angle shot image shows no brain hemosiderin deposits. **C**, **D** Unenhanced Turbo Spin Echo T1-weighted images in supra-tentorial and sub-tentorial regions show the presence of multiple intra-axial hyperintense signal lesions involving also the perivascular spaces, as for melanotic pattern. **E**, **F** Enhanced Turbo Spin Echo T1-weighted images in supra-tentorial and sub-tentorial regions show post-contrast impregnation of the multiple intra-axial lesions described in C and D. **G** Enhanced three-dimension magnetization-prepared rapid gradient-echo T1-weighted image confirms the presence of multiple intra-axial supra- and sub-tentorial lesions with post-contrasts impregnation; the cervical spinal cord included in the study shows no signal alterations

ipilimumab and nivolumab and to perform a whole-brain irradiation.

Discussion

Malignant melanoma frequently metastasizes to the central nervous system (CNS), representing the third most common cause for CNS metastases after breast and lung cancer [6], but only about 5% of the patients with melanoma metastases have more than five intracerebral metastatic lesions [7].

In a recent review, only 26 cases of miliary CNS metastases have been reported and none of these cases were related to melanoma; the most frequent primary tumor was lung (61.54%), followed by breast and unknown origin, with 11.54% each [8].

In general, risk factors for CNS metastases among patients with malignant melanoma are: male, head and neck or oral primary lesion, primary tumor thickness, ulceration of primary lesion and the presence of visceral metastases [7]. Moreover, the introduction of immunotherapies and BRAF/MEK targeted therapies have dramatically improved the survival in patients with metastatic melanoma, thus increasing the time in which CNS complications may manifest [9].

The etiology of CE is not fully known [8], but probably the BRAF V600E mutated could play a role in the onset of CE related to melanoma [5]; other research is needed to assess the possible role of this gene in the CE pathogenesis.

The clinical presentation of miliary brain metastases can vary, but the most frequent symptoms are the cognitive impairment and the subacute dementia. The great variety of symptoms observed is the consequence of the multifocal involvement of cortical and subcortical structures [8, 10]. In general, the median interval from initial diagnosis of malignant melanoma and the onset

of neurological symptoms due to CNS involvement is 3.5 years [7]. In our case, neurological findings occurred almost 9 years later and were characterized by cognitive-motor slowing without evidence of focal deficits, improved after corticosteroid administration.

Imaging plays a crucial role for differential diagnosis in patient with neurological symptoms [11, 12] and for the non-invasive diagnosis of CE. The diagnosis is made primarily by contrast-enhanced brain MRI, which has a better sensitivity than contrast-enhanced head CT [5], as seen in our case where MRI showed the actual disease burden. Melanoma brain metastasis may have heterogeneous and different appearances and locations in the head [13, 14], especially in the CNS, with typical (melanotic and amelanotic) and atypical imaging patterns [15]; melanotic pattern consists of lesions with high signal intensity on unenhanced T1-weighted images and low signal intensity on T2-weighted images, mainly due to effects of both free radicals in melanin as well as blood products; amelanotic pattern consists of lesions which are hypointense or isointense to the cortex on unenhanced T1-weighted images and hyperintense or isointense to the cortex on T2-weighted images. In CE, lesions are usually small and distributed ubiquitously, with the predominant involvement of the cortical grey matter and of the basal ganglia, as seen in our case. In all cases, administration of contrast agent to demonstrate enhancement of lesions is essential.

Miliary enhancement is generally used to describe a pattern of multiple punctate uniform enhancement with monomorphic dot-like lesions (diameter < 3 mm) and this pattern may be related to several pathologies such as metastatic disease (such as CE), CNS lymphoma, neurosarcoidosis, Erdheim–Chester disease, vitamin B12 deficiency, CNS vasculitis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, neuromyelitis optica spectrum disorders, glial fibrillary acidic protein meningoencephalomyelitis, Behçet's disease, infectious disease and Susac's syndrome. In a recent review a diagnostic algorithm in patient with brain miliary enhancement is proposed to narrow down differential diagnoses and to minimize the use of invasive diagnostic procedures [16]. In many of these cases, the diagnosis is radiological according to age, sociodemographic information, medical history and physical examination, imaging findings (localization, PVS involvement, hemorrhagic lesions, meningeal enhancement, spinal cord involvement) and the responsiveness in variable degrees to corticosteroid therapy. In particular, in adult populations, metastases presenting as diffuse miliary spread of punctate tumor nodules within or outside PVS (as in our case) should always be considered in the differential diagnosis before thinking about less frequent pathologies. In our case, moreover, the presence of lesion's signal hyperintensity on unenhanced T1-weighted sequences without signs of bleeding on T2*-weighted sequences, further confirmed the radiological diagnosis of melanoma metastases.

In general, miliary brain metastases are associated with a poor prognosis; the survival in terms of duration and quality of life depends on the extent of metastatic disease and response to treatment. Due to its low incidence, there are currently no guidelines for CE treatment. Melanoma brain metastases can be treated with surgery and/or stereotactic radiosurgery, but only when the disease is limited to few lesions; treatment for patients with multiple metastases includes whole-brain irradiation and immunotherapy [7, 17].

In conclusion, miliary brain metastases should be suspected in all melanoma patients with new neurological findings and contrast-enhanced MRI should be performed to assess the real burden of the disease.

Abbreviations

CNS	Central nervous system
CE	Carcinomatous encephalitis
WB-CT	Whole-body computed tomography
MRI	Magnetic resonance imaging
PVS	Perivascular spaces

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Not applicable.

Author contributions
MP and DV drafted the manuscript. CAM and CCQ revised the paper. All authors read and approved the final manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was waived by the local Ethics Committee in view of the descriptive nature of the study and all the procedures being performed were part of the routine care.

Consent for publication
Written informed consent for the use of existing anonymized data for research purposes was obtained from the patient as an institutional policy.

Competing interests
The authors declare that they have no competing interests.

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