Article published online: 2024-12-11

Analysis of the Molecular Profile of Melanoma Brain Metastases using Immunohistochemistry

Análise do perfil molecular das metástases cerebrais de melanoma no exame de imuno-histoquímica

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Arq Bras Neurocir 2024;43(4):e258–e261.

Abstract

Brain metastases from melanoma represent an advanced and aggressive form of the disease. Understanding their molecular characteristics is crucial for improving diagnosis, prognosis, and treatment. The main objectives of this study were to identify and characterize molecular alterations present in brain metastases from melanoma and to clinically correlate them. The clinical-epidemiological information was anonymously and retrospectively obtained. Brain metastases from melanoma were collected through surgical biopsies, which were processed and analyzed using immunohistochemical markers. A total of 132 samples were initially selected, resulting in 8 samples of metastatic melanoma in the brain region included in this analysis. Regarding the frequency of immunohistochemical markers in brain samples of melanoma metastasis, 75% showed positive BRAF V600R, 62% contained positive SOX10, 37% positive HMB45, and 25% positive Melan-A. Regarding the location, 4 of them were in the frontal lobe, 3 in the parietal lobe, and 1 in the cerebellum. Among the samples, 87.5% originated from the supratentorial region of the brain, while 12.5% came from the infratentorial region. At the time, half of the patients were under 65 years old, with a significant proportion of 25% of individuals being below 40 years old. Moreover, 87.5% had two or more brain lesions at the time of diagnosis. Among the 12.5% that comprised the single lesion group at the time of analysis, the frontal lobe location

Keywords

- neurosurgery
- brain metastase
- immunohistochemistry

Instituição de realização do trabalho: AC Camargo Cancer Center, São Paulo, São Paulo, Brasil.

received
May 9, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796655.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

stands out. The findings indicate heterogeneity among tumors and metastases in different anatomical locations. Further investigations are needed to validate these findings and elucidate their clinical applicability.

Resumo

As metástases cerebrais de melanoma representam uma forma avançada e agressiva da doença. Compreender suas características moleculares é crucial para melhorar o diagnóstico, prognóstico e tratamento. Os principais objetivos deste estudo foram identificar e caracterizar as alterações moleculares presentes nas metástases cerebrais de melanoma e correlacioná-las clinicamente. As informações clínico-epidemiológicas foram obtidas anonimamente e retrospectivamente. As metástases cerebrais de melanoma foram coletadas por meio de biópsias cirúrgicas, que foram processadas e analisadas utilizando marcadores imuno-histoquímicos. Um total de 132 amostras foram inicialmente selecionadas, resultando em 8 amostras de melanoma metastático na região cerebral incluídas nesta análise. Em relação à frequência dos marcadores imuno-histoquímicos nas amostras cerebrais de metástase de melanoma, 75% apresentaram BRAF V600R positivo, 62% continham SOX10 positivo, 37% HMB45 positivo e 25% Melan-A positivo. Quanto à localização, 4 delas estavam no lobo frontal, 3 no lobo parietal e 1 no cerebelo. Entre as amostras, 87,5% originaram-se da região supratentorial do cérebro, enquanto 12,5% provinham da região infratentorial. No momento, metade dos pacientes tinha menos de 65 anos, com uma proporção significativa de 25% de indivíduos abaixo de 40 anos. Além disso, 87,5% tinham duas ou mais lesões cerebrais no momento do diagnóstico. Entre os 12,5% que compunham o grupo de lesão única no momento da análise, destaca-se a localização no lobo frontal. Os achados indicam heterogeneidade entre tumores/metástases em diferentes locais anatômicos. Mais investigações são necessárias para validar esses achados e elucidar sua aplicabilidade clínica.

Palavras-chave
- neurocirurgia
- metástases cerebrais
- imuno-histoquímica

Introduction

Melanoma is a type of skin cancer that can spread to other tissues, including the central nervous system. This stage represents an advanced stage of the disease and is associated with an unfavorable prognosis. Understanding the molecular characteristics of brain metastases from melanoma is essential for the diagnosis, treatment, and prognosis of these patients.[1]

The incidence of melanoma is 100,000 new cases per year in the United States alone. Among patients with advanced melanoma, approximately 50% develop brain metastases, resulting in significant morbidity and mortality. Local therapy, including surgery and radiation, has historically resulted in an overall survival of 4 to 6 months for patients with melanoma brain metastases.[2]

Until now, primary melanomas have been extensively studied; in contrast, the biology of melanoma brain metastasis remains poorly understood. There is increasing evidence of the emergence of metastatic tumor clones in the central nervous system distinct from the primary site throughout tumor progression. This tumoral heterogeneity occurs in more than 50% of cases and may drive the development of metastatic disease as well as resistance to cancer therapy.[3]

Immunohistochemistry is a widely used technique in the molecular characterization of different types of cancer. It involves the detection of specific proteins in tissue samples using antibodies that bind to these proteins of interest. This technique provides information about the molecular profile of the sample and aids in the identification of potential therapeutic targets.[4,5]

Understanding the molecular alterations present in these lesions can provide insights into tumor biology, enabling the identification of specific molecular markers and the development of more targeted therapeutic strategies.[6]

In this context, this research aimed to investigate the molecular profile of melanoma brain metastases through immunohistochemistry examination, aiming to identify the expressions of key proteins involved in melanoma brain metastases, as well as to identify the age, location, and number of lesions in the collected samples, allowing for the acquisition of relevant information for patient stratification and selection of targeted therapies.

Methods

A retrospective observational study was conducted through the review of anonymous databases of patients from AC Camargo Cancer Center diagnosed with

Sample	Age	Localization	2 or more lesions	Positive markers
16024821	46	left front	yes	BRAF V600E
96015659	78	left front	yes	BRAF V600E SOX10 Melan A HMB45
14889910	65	right parietal	yes	S100 HMB45 Melan A
14793550	39	right parietal	yes	BRAF V600E SOX10
14834070	65	right front	no	BRAF 600? SOX10
16029252	59	left parietal	yes	BRAF V600E SOX10
16027675	75	right front	yes	BRAF V600E – HMB45 S100
13960510	38	cerebellum	yes	BRAF V600E SOX10

Fig. 1 Characteristics of melanoma brain metastasis samples.

metastatic brain tumors with a primary focus on melanoma who underwent biopsy or surgery followed by immunohistochemistry examination from March 2022 to November 2023, aiming to collect clinical and histopathological data. The anonymous database was analyzed, and the data were collected in an academic environment from September to October 2023. All data are confidential, and no participant names or any other form of identification are exposed.

The present study will analyze the markers BRAF V600E, SOX 10, HMB45, and Melan-A. These are the most common alterations observed among metastatic melanoma samples in previous studies in the field. As the study is retrospective, the listed markers are already specified in the issued reports, and no new tests or samples will be manipulated or conducted from the present date. The pathology medical professional will have already been designated at the time of the report when the individual was under treatment. Only the data from the tests conducted during the period will be collected and analyzed.

The inclusion criteria used were samples from participants aged 18 years or older, admitted to the AC Camargo Cancer Center with a diagnosis of metastatic brain tumor with a primary focus of melanoma, subjected to biopsy or surgery, followed by immunohistochemical examination. As exclusion criteria, results from non-melanoma brain metastases, participants outside the age range, and/or those without the immunohistochemical examination were used.

Results

A total of 132 samples of melanoma metastases were initially selected, resulting in 8 samples of metastatic melanoma in the cerebral location that were included in this analysis. Age, location, number of brain lesions, and the markers present in the immunohistochemical sample were collected (►**Fig. 1**).

Regarding the location, 4 of them were in the frontal lobe, 3 in the parietal lobe, and 1 in the cerebellum. Among the samples, 87.5% originated from the supratentorial region of the brain, while 12.5% came from the infratentorial region.

Regarding the age of the individuals at the time of sample collection for analysis, half of them were below 65 years old, with a notable 25% of individuals falling below the age range of 40 years old.

Regarding the number of lesions observed on imaging exams at the time of diagnosis, 87.5% had one or more brain lesions. Among the 12.5% that comprised the single lesion group at the time of analysis, the location in the frontal lobe stands out.

The frequency of immunohistochemistry markers (►**Fig. 2**) in samples of brain metastatic melanoma tumors showed 75% tested positive for BRAF V600R, 62% for SOX10, 37% for HMB45, and 25% for Melan-A.

Discussion

Brain metastases result in significant mortality and morbidity for patients with advanced melanoma. A better understanding of the biology of melanoma brain metastases remains an

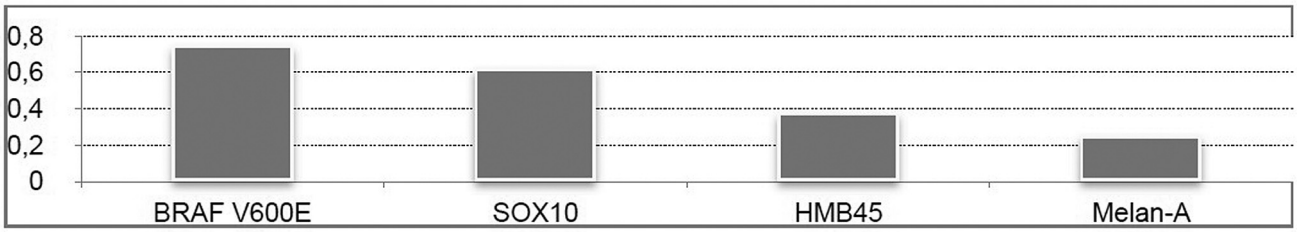

Fig. 2 Frequency of immunohistochemistry markers in brain metastasis samples.

unmet need. The age of the individual at the time of tissue sample collection, with 25% of them falling below the age of 40, highlights a progressive decrease in the average age at the time of cancer diagnosis, currently standing at 62 years.[7]

The location of brain metastases predominantly occurs in the supratentorial region of the brain, consistent with recent studies on the subject. The BRAF V600E marker was the most prevalent in the analyzed samples, similar to what has been described in the literature.

It is important to highlight the limitations of this study. Clinical data were retrieved from medical records through a retrospective analysis over time, so information on the progression and identification of the primary focus of melanoma in some cases was not found, and the diagnosis was defined through tissue analysis of the brain metastasis after surgery.

Conclusion

The retrospective analysis of tissue samples from metastatic melanoma tumors in the brain through immunohistochemistry demonstrated that the most prevalent markers present were BRAF V600E, SOX10, HMB45, and Melan-A. The preferred anatomical location of the lesions was the supratentorial region of the brain, more specifically in the frontal lobe. Our findings corroborate the existence of heterogeneity among tumors/metastases in different anatomical locations. Further investigations are needed to validate these findings and elucidate their clinical applicability.

Disclosures
The author declares that no relevant or material financial interests relate to the research described in this paper.

Conflict of Interest
The author declares no conflict of interest.

References

1 Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro-oncol 2017;19 (11):1511–1521
2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(01):7–34. Doi: 10.3322/caac.21551
3 In GK, Poorman K, Saul M, et al. Molecular profiling of melanoma brain metastases compared to primary cutaneous melanoma and to extracranial metastases. Oncotarget 2020;11(33):3118–3128. Doi: 10.18632/oncotarget.27686
4 Sloan AE, Nock CJ, Einstein DB. Diagnosis and treatment of melanoma brain metastasis: a literature review. Cancer Control 2009;16(03):248–255
5 Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379(08):722–730
6 Tawbi H, Forsyth P, Hodi S, Lao C. Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). J Clin Oncol 2019;37(15):9501–9501
7 Internò V, Sergi MC, Metta ME, et al. Melanoma Brain Metastases: A Retrospective Analysis of Prognostic Factors and Efficacy of Multimodal Therapies. Cancers (Basel) 2023;15(05):1542. Doi: 10.3390/cancers15051542

