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Malignant melanoma – the most severe skin cancer and neurological pathology

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Abstract

Objective: We report our clinical experience with malignant melanoma (MM) patients associated with neurological involvement. *Patients, Materials and Methods*: A database of patients admitted from 2014–2019 in the I[st] Clinic of Neurology, Emergency County Hospital of Târgu Mureş, Romania, was reviewed to identify patients with MM and neurological involvement. We assessed the demographic and clinical data regarding the neurological disorders and the primary tumor characteristics from the patient registries. Both histopathological and immunohistochemical analysis of the neoplasm was available for the entire cohort. *Results*: We analyzed 13 982 patient files and 21 met all the inclusion and exclusion criteria. Brain metastases were found in 38.09% of the patients, spinal metastases in 9.52% of the patients, ischemic stroke by cancer-associated thrombosis in 42.85% of the patients and peripheral nervous system involvement in 19.04% of the patients. No statistically significant differences between the four categories of neurological disorders according to socio-demographic parameters, location of the primary tumor, existence of primary tumor ulceration, invasion of the lymph nodes or the presence and location of distant metastasis was found ($p>0.05$). Our presented patient is the first case of uveal melanoma with hemorrhagic brain metastasis before hepatic involvement. *Conclusions*: Neurological involvement in MM encompasses a myriad of variants and while the clinical setting varies from one patient to another, an underlining neoplasia should be evaluated in suspected patients.

Keywords: malignant melanoma, brain metastasis, spinal metastasis, stroke, polyneuropathy.

Introduction

Malignant melanoma (MM) represents a type of cancer that develops from the uncontrolled proliferation of melanocytes. Melanocytes originate from the neural crest cell during embryonic development and migrate in the epidermis, and various other sites, widely distributed along cranio-spinal axis. These cells specialized in producing pigment can be found in epidermis, but also in other extra-cutaneous pigment containing tissue, such as meninges, eyes and mucous membranes. Thus, there are three MM subtypes: cutaneous melanoma (CM), the most common subtype, uveal melanoma (UM) and mucosal melanoma [1, 2].

MM is the most aggressive skin cancer. In the last decades, the incidence and rates of mortality are constantly increasing worldwide within the white population [3–6]. Different from the other solid malignancies, MM is more frequent in younger patients with a mean again the sixth decade at the moment of MM diagnosis and with a female predominance in younger age groups [7]. Mortality rates in melanoma are influenced by the geographical location (highest rates in low-latitude regions/North America, Australia, Northern Europe), age, gender (higher mortality in male patients) and ethnicity (higher in non-Hispanic Caucasians) [5, 8, 9]. In younger patients, MM is responsible for early metastasis [3, 10].

Aim

Given the great variability of MM manifestations in neurological patients, we aimed to investigate and to analyze the frequency and the type of the neurological complications secondary to MM patients in a large cohort of patients admitted to our Clinic in a 10-year time frame.

Patients, Materials and Methods

Patients' group selection

We performed a retrospective population-based cohort study. In order to select the eligible patients for the study, we used the database of the I[st] Clinic of Neurology, Emergency County Hospital of Târgu Mureş, Romania. All the admissions and medical letters between January 1, 2014 and October 1, 2019 were verified. The following inclusion criteria were used: (*i*) patients >18 years old; (*ii*) diagnosis of MM at the time of admission, during the hospitalization in the Clinic of Neurology or in the patient history; (*iii*) available morphopathological examination of the primary tumor, with a diagnosis of MM; (*iv*) the presence of neurological manifestations secondary

to the cancerous disease. The exclusion criteria were: (*i*) patients without diagnosis of MM at the time or during hospitalization in the Clinic of Neurology or in the patient's history; (*ii*) patients diagnosed with MM, but without secondary neurological impairment; (*iii*) the causal relationship between MM and neurological disorder could not be established with certainty.

The demographic data of the patients (age, gender, origin) and data related to neurological disorders, respectively those related to MM profile (location of primary tumor, presence or absence of ulceration, lymph node involvement, presence of distant metastases and their location) were taken from the patient observation sheet.

Depending on the neurological condition secondary to MM, the patients were classified into four categories: (*i*) brain metastases; (*ii*) spinal metastases; (*iii*) ischemic stroke secondary to cancer-associated thrombosis; (*iv*) peripheral nervous system involvement. The characteristics of the primary tumor for each of the four categories were analyzed to try to outline the profile of the MM that is associated with each of the four categories of neurological disorders mentioned.

The diagnosis of cerebral and spinal metastasis was established by the use of cerebral and spinal imaging by 1.5 T magnetic resonance imaging (MRI). The ischemic stroke secondary to cancer-associated thrombosis diagnosis was established based on cerebral computed tomography (CT) and MRI, and the exclusion of other possible causes (cardioembolic, atherosclerotic, autoimmune, hereditary hypercoagulability syndrome). The involvement of the peripheral nervous system was established based on electroneuromyography.

Histopathological and immunohistochemical analysis

The specimens were all fixed in 10% neutral buffered formalin and further processed according to routine practice guidelines. Five-µm-thick sections were stained with Hematoxylin–Eosin (HE). Special stainings to differentiate the melanin pigment (Fontana–Masson staining kit) from iron pigment (Perl's Prussian Blue Iron staining kit) were also used.

Immunohistochemistry was performed on four-µm-thick sections, using anti-S100 (1:100, clone IR504, Dako, Glostrup, Denmark) and anti-human melanoma black 45 (HMB45) (1:100, clone HMB45, Novocastra, Newcastle upon Tyne, United Kingdom) antibodies. For heat-induced antigen retrieval, the sections were subjected to incubation with high-pH buffer (pH 9) for 30 minutes. The developing was performed with 3,3'-Diaminobenzidine (DAB) solution (Novocastra) and counterstaining was done with Mayer's Hematoxylin (Novocastra). For negative controls, incubation was done with omission of specific antibodies. Appropriate positive controls were simultaneously performed for both tested antibodies.

Statistical analysis

The data were entered into an Excel table and the statistical analysis of the data was performed using the χ^2 (*chi*-square) test. We interpreted all tests against a p=0.05 significance threshold and statistical significance was considered for p-values less than the significance threshold.

Ethics approval

The study was approved by the local Ethics Committee of the Emergency County Hospital of Târgu Mureş (Approval No. 34950/2019).

Results

In the Ist Clinic of Neurology, Emergency County Hospital of Târgu Mureş, 13 982 patients were admitted between January 1, 2014 and October 1, 2019. We identified a number of 21 (0.15%) patients who met the inclusion and exclusion criteria for the current study.

Regarding neurological manifestations, brain metastases were found in eight (38.09%) patients, spinal metastases in two (9.52%) patients, ischemic stroke by cancer-associated thrombosis in nine (42.85%) patients and peripheral nervous system involvement in four (19.04%) cases. We mention that one of the patients had both cerebral and spinal metastases, while another patient had cerebral metastases and signs of peripheral nervous system involvement. Of the eight patients with cerebral metastases, four had multiple hemorrhagic metastases, two unique hemorrhagic metastases, and two cerebral metastases without hemorrhagic transformation. Regarding the localization of cerebral metastases, we observed the following: frontal localization in four patients, parietal in three patients, temporal in two patients, cerebellar in two patients, brainstem in one patient. In four of the eight patients with brain metastases, the neurological symptomatology was the first manifestation of the primary tumor, the diagnosis of MM being subsequently established. The cerebral lesions had variable sizes, with the minimum of 0.2 cm and the maximum of 4.4 cm, most of them being surrounded by digitiform perilesional edema. Regarding the patients with peripheral nervous system involvement, three patients had chronic inflammatory demyelinating polyneuropathy (CIDP), and one axonal sensory-motor polyneuropathy.

In terms of gender distribution, 10 men and 11 women were included in the study. The average age of the patients was 66.04 years. Regarding the origin environment, eight (38.09%) patients come from the rural area and 13 (61.91%) from the urban area (assuming more sun exposure in patients from rural area). We did not identify any statistically significant difference between the four categories of neurological disorders according to the distribution by gender, age group, or place of origin (p=0.43, p=0.52, and p=0.31, respectively). All of the patients' demographic data are found in Table 1.

The localization of the primary tumor was as following: upper and lower limbs in three (14.28%), face in two (9.52%), ocular in two (9.52%), head (scalp) and neck in seven (33.33%), trunk in four (19.04%), abdomen in three (14.28%) patients. All cases were diagnosed as nodular melanoma, with a median Breslow tumor thickness of 4.3 mm. Most of the cases were Clark level IV (20 cases, 95.24%) and one case (4.76%) was Clark level V. There was no significant difference in Breslow tumor thickness and Clark level between men and women. The epithelial ulceration and a high mitotic index [more than 10 mitoses/ high-power field (HPF)] were present in all cases. We did not identify any statistically significant difference

between the four types of neurological manifestations regarding the location of the primary tumor (p=0.1). The presence of skin ulcerations was found in five (23.8%) of the cases. The lymph node involvement was described in five (23.8%) patients. Most of the patients had no other distant metastases – 18 (85.71%). The most frequent distant metastases were found in the lung, in three (14.28%) of the cases. All this data can be found in Table 2. There were no statistically significant differences regarding the presence or absence of primary tumor ulceration (p=0.41), invasion of the lymph nodes (p=0.43), the presence of distant metastases (p=0.27), or their location (p=0.87), nor the type of treatment followed until the onset of neurological symptoms (p=0.56).

Table 1 – ***The demographic data of the patients included in the study as a whole and separated according to the neurological manifestations***

Neurological manifestations	Overall	Cerebral metastases	Spinal metastases	Ischemic stroke secondary to cancer-associated thrombosis	Peripheral nervous system involvement	*p*-value
No. of patients (%)	21	8 (38.09%)	2 (9.52%)	9 (42.85%)	4 (19.04%)	
Gender						
Males	10 (47.62%)	4	0	5	1	0.43
Females	11 (52.38%)	4	2	4	3	
Median age [years] (mean)	66.04	66.62	57.5	68.77	62.75	0.53
Age group						
20–45 years	0 (0%)	0	0	0	0	0.52
46–55 years	4 (19.04%)	2	1	1	1	
56–65 years	5 (23.8%)	0	1	2	2	
66–75 years	9 (42.85%)	5	0	4	0	
76–85 years	2 (9.52%)	1	0	1	1	
>85 years	1 (4.76%)	0	0	1	0	
Place of origin						
Rural	8 (38.09%)	3	0	3	3	0.31
Urban	13 (61.91%)	5	2	6	1	

Table 2 – ***Descriptive table of the factors related to the primary tumor (malignant melanoma) for the whole group of patients, and stratified according to the neurological manifestations***

Neurological manifestations	Overall (*n*=21)	Cerebral metastases (*n*=8)	Spinal metastases (*n*=2)	Ischemic stroke secondary to cancer-associated thrombosis (*n*=9)	Peripheral nervous system involvement (*n*=4)	*p*-value
Body site (%)						
Upper and lower extremities	3 (14.28%)	1	1	0	2	0.1
Face	2 (9.52%)	1	0	1	0	
Ocular	2 (9.52%)	1	1	0	0	
Head (scalp) and neck	7 (33.33%)	2	0	5	1	
Trunk	4 (19.04%)	0	0	3	1	
Abdomen	3 (14.28%)	3	0	0	0	
Unspecified	0 (0%)	0	0	0	0	
Skin ulcerations (%)						
Present	5 (23.8%)	1	0	2	2	0.41
Absent	16 (76.19%)	7	2	7	2	
Lymph node involvement (%)						
Present	5 (23.8%)	2	1	1	2	0.43
Absent	16 (76.19%)	6	1	8	2	
Distant metastases (%)						
Present	3 (14.28%)	2	1	0	1	0.27
Absent	18 (85.71%)	6	1	9	3	
Distant metastases (%)						
Lung	3 (14.28%)	2	1	0	1	0.87
Bones	1 (4.76%)	1	0	0	0	
Liver	1 (4.76%)	1	1	0	0	
Spleen	1 (4.76%)	1	1		0	
Treatment (%)						
Surgery	16 (76.19%)	5	1	8	4	0.56
Radiotherapy	3 (14.28%)	2	1	1	0	
Chemotherapy	3 (14.28%)	2	1	0	1	
None	5 (23.8%)	3	1	1	0	

Of all the cases included in the study, we present the case of a 70-year-old patient with hypertension, without any other significant pathological personal history, who suddenly presents on the day of admission in our Clinic with marked headache, balance disorders, nausea and vomiting. General physical examination was normal, except for a blood pressure of 170/100 mmHg. The neurological examination at admission revealed marked gait and truncal ataxia, dysmetria and tremor at finger-to-nose and heel-knee-shin tests on the left side, with no other features. The cerebral CT examination performed in the Emergency Department revealed a cerebellar hematoma with vermian localization with dimensions of 20/10 mm (Figure 1, a and b). The case was initially interpreted as a spontaneous cerebellar hematoma in a patient with elevated blood pressure. Under cerebral depletive treatment, the neurological condition of the patient remained stationary, and the control CT scan performed at two weeks revealed the lack of resorption of the hemorrhagic lesion (Figure 1, c and d). At three months after onset, the neurological symptomatology of the patient remained stationary, which is why a cerebral MRI examination was performed that revealed in the cerebellar vermis a hypointense T2-weighted and hyperintense T1-weighted lesion, 28/18 mm in diameter (Figure 2, a and b).

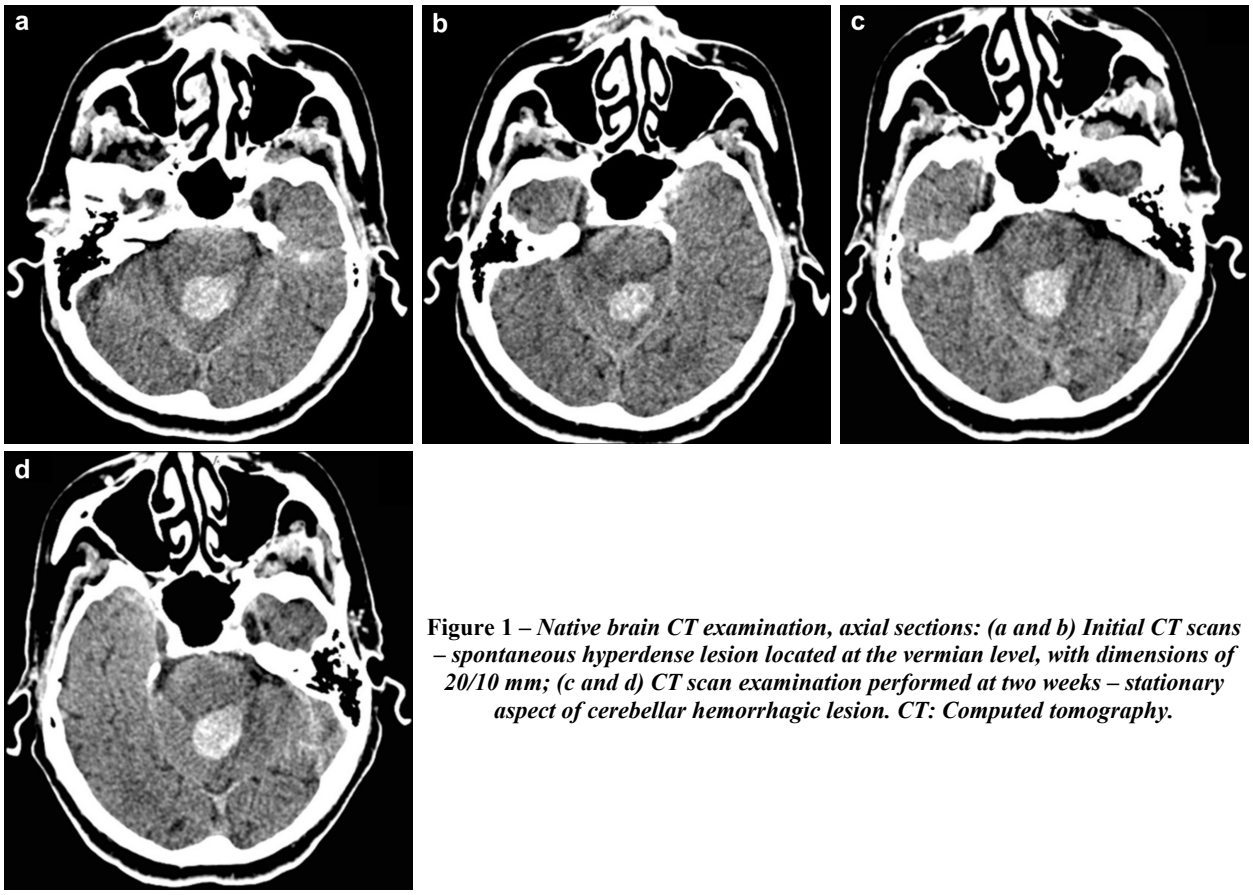

Figure 1 – ***Native brain CT examination, axial sections: (a and b) Initial CT scans – spontaneous hyperdense lesion located at the vermian level, with dimensions of 20/10 mm; (c and d) CT scan examination performed at two weeks – stationary aspect of cerebellar hemorrhagic lesion. CT: Computed tomography.***

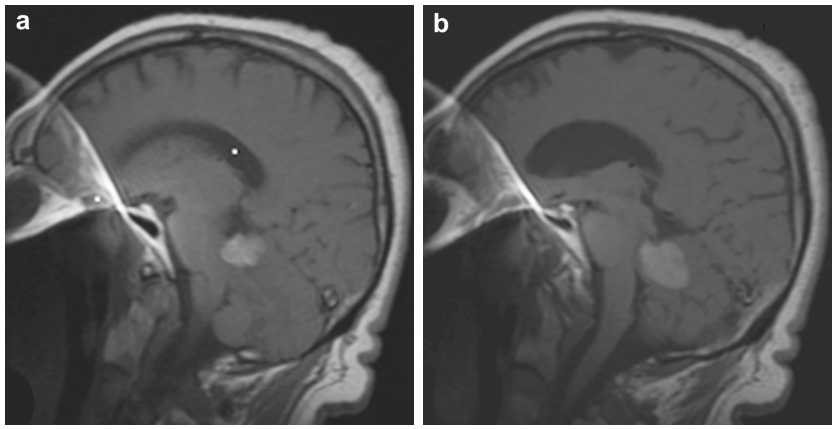

Figure 2 – ***Native MRI of the brain (sagittal view) showing a T1 hyperintense lesion located in the vermis, measuring 22/18 mm, without associated edema, compressing the fourth ventricle. MRI: Magnetic resonance imaging.***

The neurosurgical intervention was performed in order to excise the hemorrhagic tumoral mass. The specimens sent to the Pathology Department consisted of multiple, large, compact, blackish tissue fragments, measuring 15 mm in the largest diameter. Upon microscopic examination, the case fulfilled the criteria for the diagnosis of melanoma cerebellar metastasis. The tumor consisted of lobular nests and sheets of poorly differentiated cells with melanotic-

and epithelioid-type features (Figure 3). HPF examination revealed large polygonal to round tumor cells with well-delimited cell borders. The cytoplasm contained melanin pigment in large amounts, highlighted also by the Fontana–Masson staining. The nuclear-to-cytoplasmic ration was high, due to the large, vesicular nuclei, with conspicuous eosinophilic nucleoli (Figure 4). Frequent atypical mitotic figures were observed (the mitotic index was 7/10 HPFs). The tumor cells were negative for iron pigment. Some interspersed connective tissue septae containing benign lymphocytes and enlarged blood vessels were also observed. The tumor cells displayed diffuse cytoplasmic positive labeling for S100 and HMB45 (Figures 5 and 6). After receiving the histopathological (HP) result, due to the fact that the primary tumor was not found at the skin level, the patient was referred to the ophthalmology clinic, and the clinical and ultrasound revealed the presence of the UM. We also performed a whole-body CT scan, which was unremarkable. The patient died 138 days after the onset of neurological symptoms due to hemorrhagic cerebellar metastasis, which was the first manifestation of MM.

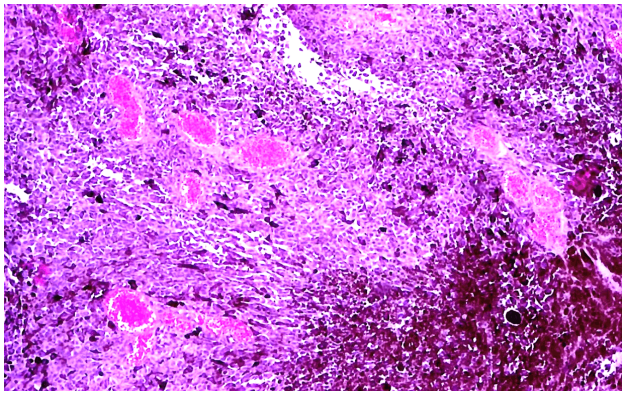

Figure 3 – ***Hematoxylin–Eosin (HE) staining showing an invasive tumor consisting of lobular nests and sheets of epithelioid cells with melanotic features, displaying large amounts of cytoplasmic melanin pigment (×100).***

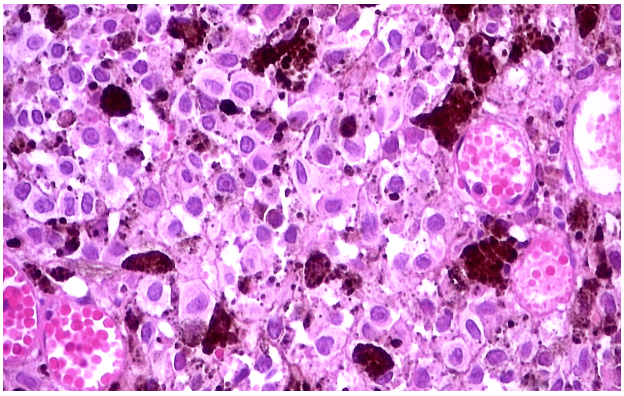

Figure 4 – ***High-power field examination revealed large polygonal to round tumor cells with well-delimited cell borders and large, vesicular nuclei, with conspicuous eosinophilic nucleoli (HE staining, ×400).***

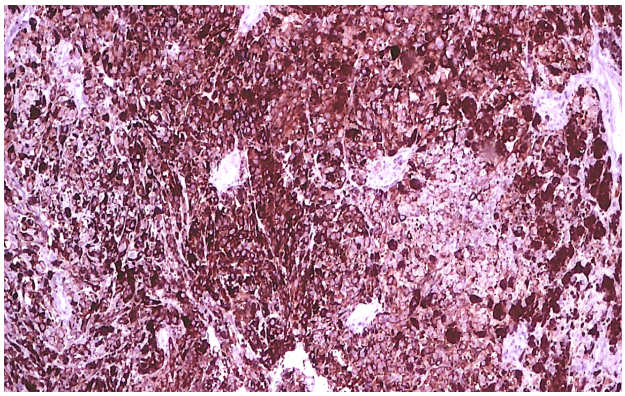

Figure 5 – ***On immunohistochemistry, the tumoral cells show strong and diffuse positive staining for HMB45 (Anti-HMB45 antibody immunomarking, ×200). HMB45: Human melanoma black 45.***

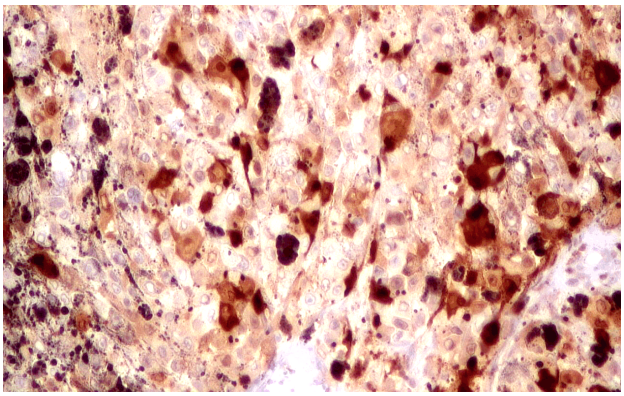

Figure 6 – ***The tumoral cells were positive for S100 (Anti-S100 antibody immunomarking, ×400).***

Discussions

Metastatic disease of the central nervous system (CNS) is a frequent complication of MM, being the third leading cause of CNS metastases, after lung and breast cancer [11]. It is associated with increased morbidity, mortality and with a poor prognosis with a median overall survival of 17–22 weeks [12–14]. Poor prognostic factors identified in patients with MM are: male patients of older age, site/localization of primary tumor, HP characteristics, biochemical measures (increased serum lactate dehydrogenase and S100 protein level) and v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) gene mutation [1, 15–19]. Skin infection with various genotypes of human papillomavirus (HPV), such as α-HPV, have been reported in the skin carcinogenesis [20].

The site of the MM was demonstrated to have important prognostic implications. The location of MM in the cephalic extremity (especially scalp location), neck and trunk region, carry a worse prognosis more prone for brain metastasis, than those from the limbs [15, 16, 21, 22].

In our group of melanoma patients with neurological manifestation, the CNS metastases (brain and spinal cord) were the most frequent neurological complications, presented in almost half of the patients. In our group, the CNS metastases were most frequently associated with melanoma in cranial region, followed by abdominal wall region. Callender *et al.* reported that the anatomic localization of the primary melanoma in the head/neck and trunk region is an important independent predictor for a worse prognosis, compared to melanoma in any other anatomic localization [22]. Huismans *et al.* found

that the patients with primary scalp melanoma are more likely to develop brain metastases than the patients with involvement of the head and neck regions [23]. From the large group of patients (13 982) that were evaluated, we identified 21 (0.15%) cases of MM with secondary neurological complications. This relatively small number of patients is due to the emergency profile of our Clinic. In our group of patients, 19% had acute deterioration of neurological condition, which led to the diagnosis of MM.

There are distinct HP features that represent poor prognostic factors, associated with a higher risk for metastases in CM patients. Increased thickness of the primary cutaneous lesion (≥4 mm) is correlated with poor survival outcomes. Presence of the epithelial ulceration in the primary lesion is the second most powerful independent factor for poor prognosis in CM [16, 24, 25]. Another significant pathological feature associated with poor prognosis is the increased mitotic rate (≥20 mitoses/mm^2) [26, 27].

The metastasis secondary to melanoma dissemination most often occur through the lymphatic system, followed by the hematogenous spread [28, 29]. The genesis of the metastases is a multi-step and complex process, as follows: initially, the tumoral cells are arrested at the vascular branch point, afterwards, the circulating tumoral cells adhere to the endothelium and bypass through the blood–brain barrier. The third step involves a close contact between the tumoral cells and the microvessels, continued by perivascular growth of tumoral cells, angiogenesis, in the end, determining secondary tumoral development within the brain [30, 31].

Hong *et al.* described the spatial distribution of the brain metastasis: the majority were located in the frontal (43%) and the parietal lobe (20%), less frequent in the cerebellum (8.6%) and very rare in the hippocampal region [32]. In a Danish study, 12% of the patients with MM had asymptomatic CNS metastases, detected by contrast-enhanced CT scan [33].

In our study, eight (38%) patients had cerebral metastasis, and most frequent location was supratentorial in the frontal and the parietal lobe, followed by infratentorial lesions (cerebellar and brainstem). We found two (9.5%) patients with spinal cord leptomeningeal metastasis and one with brain and spinal cord metastasis. Spinal cord metastases are intradural extramedullary secondary tumors and they have a worse prognosis compared to brain metastases, with median survival time without treatment of 4–6 weeks. Malignant cells reach the cerebrospinal fluid through several routes: hematogenous, direct extension, venous access, respectively from cranial and peripheral nerves [34, 35].

Choroid/uveal melanoma is the most common primary intraocular malignancy, an uncommon disease associated with poor prognosis and treatments resistance [36, 37]. The median age at diagnosis is 55 years and is slightly more frequent in men [38]. This type of MM most often metastases through the hematogenous way into the liver, and in contrast CM spreads first to lymph nodes with a lower incidence of hepatic diffusion [39, 40]. Brain metastases of UM are very rare, usually are diagnosed after or concomitant to liver metastases and have a reserved prognosis [41, 42]. Our presented patient is the first reported case in medical literature with hemorrhagic brain metastases as initial clinical manifestation of an UM, without liver metastases and with very poor prognosis.

Approximately 39% of the patients with MM develop brain metastases [43]. Usually, these are multiple, located especially supratentorial and frequently with hemorrhagic transformation [44]. Patients with cerebral metastases secondary to MM have a median survival rate of 113 days [45, 46]. In our case, the patient had as the first manifestation of the MM the cerebellar hemorrhagic metastasis, and the survival from the onset of the symptoms was 138 days.

Cerebral metastases secondary to MM have various morphopathological characteristics and multiple degrees of pigmentation. In the case of our patient from a morphopathological point of view, the epithelioid type cells predominate with large amounts of melanin pigment in the cytoplasm. Frequent atypical mitotic figures, a high mitotic activity and the presence of necrosis predispose this type of brain metastasis to hemorrhagic transformation [46].

In the differential diagnosis of cerebral hemorrhagic metastases, we should consider primary neoplasia arising from the lungs, kidneys, thyroid and choriocarcinoma [47]. In terms of imaging, MM metastases can be classified in melanotic or amelanotic, depending on the degree of pigmentation. At the brain MRI examination, the melanotic ones appear as hyperintense T1-weighted and hypointense T2-weighted images relative to gray matter, and the amelanotic ones appear as other cerebral tumors, iso- to hypointense in T1-weighted images and iso- to hyperintense in T2-weighted images relative to the cortex [46]. In our patient's case, brain imaging correlates with the result of HP examination, the imagistic aspect meeting the criteria for a melanocytic lesion, as confirmed by the morphopathological examination.

Increasing evidence supports the knowledge that cancer increases the arterial thromboembolism risk; therefore, cancer-associated stroke is accepted to be common in this category of patients [48]. The interrelationship between these two pathologies is a complex one. Although cardiovascular risk factors (hypertension, diabetes, smoking, hyperlipidemia) are the most common underlying cause of stroke in cancer patients, there are specific cancer-related mechanism that can further increase the risk of stroke: hypercoagulability state with cancer-associated thrombosis induced by factors secreted by tumor cells, non-bacterial thrombotic endocarditis or cancer treatment-related side effects [49]. Tumoral cell secrete cytokines, which directly or indirectly activate coagulation cascade and inhibit the normal anticoagulant molecules, determining stroke in cancer patients [50, 51]. The risk of this association is increased in lung, pancreatic and colorectal cancer, and there are no data in the literature about the association of stroke in MM patients. In our study group, stroke was present in nine (42.85%) patients.

MM is a potentially immunogenic neoplasia, and tumor-specific antigens, that are used as targets of immunotherapy in melanoma, are surface glycoproteins that have similar immunogenic phenotype with the glycoproteins on the surface of the myelin and the axons from peripheral nerves. MM can induce either acute or chronic

autoimmune neuropathies, paraneoplastic disease of peripheral nervous system, determined by a cross reactivity between melanoma and peripheral nerve antigens. Most frequent forms of neuropathy associated with MM were CIDP, followed by axonal motor neuropathy [52–55]. In our studied patients, the most frequent form of neuropathy associated with MM was CIDP in 75% of cases and axonal sensory-motor polyneuropathy in 25% of patients.

Conclusions

The present paper enriches the contemporary data regarding the diagnosis, evolution and prognostic of neurological implications in MM in the universal health care setting, by appending to the available international knowledge. In our group of patients, the most frequent neurological manifestations secondary to the MM were the CNS metastases, in most cases multiple and with hemorrhagic transformation, with predominantly supratentorial localization in the frontal and parietal lobes. When faced with a patient with multiple hemorrhagic metastases, MM should be ruled out.

Conflict of interests

The authors declare no conflict of interests.

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