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MMP1, MMP9, MMP11 and MMP13 in melanoma and its metastasis – key points in understanding the mechanisms and celerity of tumor dissemination

BOGDAN STELIAN MASTALIER MANOLESCU[1,2], ANGELA MĂDĂLINA LAZAR[2,3], GEORGE SORIN ŢIPLICA[4], SABINA ANDRADA ZURAC[5], ADRIAN REBOŞAPCĂ[6], BOGDAN ANDREESCU[6], CRISTIANA GABRIELA POPP[5]

[1]*Department of General Surgery, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[2]*Department of General Surgery, Colentina Clinical Hospital, Bucharest, Romania*

[3]*Department of Functional Sciences, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[4]*Department of Dermatology II, Colentina Clinical Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[5]*Department of Pathology, Colentina Clinical Hospital, Bucharest, Romania*

[6]*Department of Plastic Surgery, Colentina Clinical Hospital, Bucharest, Romania*

Abstract

Background: Matrix metalloproteinase (MMP)1, MMP9, MMP11, and MMP13 are overexpressed in malignant melanoma (MM), being associated with tumor invasive phase, metastases, and more aggressive neoplastic phenotypes. *Aim*: The main objective of the current study was to correlate the expression of the MMPs with the evolution of MM toward distant metastasis. *Patients, Materials and Methods*: We designed a retrospective cohort study, including 13 patients with metastatic MM. Data concerning age, sex, localization of the primary lesion and metastasis, and histological and immunohistochemical features (intensity of expression and percent of positive cells for MMPs) were statistically processed. *Results*: The time between the diagnosis of primitive melanoma and the diagnosis of metastasis ranged between 0 and 73 months, with a mean value of 18.3 months. The metastases rich in MMP1- and MMP9-positive cells occurred earlier than the metastases with low levels of positive cells. The mean period until metastasis was shorter for the MMP1-expressing tumors than the ones without MMP1 expression. MMP13 expression in the tumor and its metastasis was significantly linked with the time until the metastasis occurrence. *Conclusions*: This study emphasizes the roles of MMP1, MMP9, and MMP13 in the process of metastasis in melanoma and the opportunity to use them as therapeutic targets and surveillance molecules.

Keywords: malignant melanoma, matrix metalloproteinases, metastases, therapeutic targets, surveillance molecules.

Introduction

Although malignant melanoma (MM) represents only 1–8% of the skin neoplasia, it is responsible for approximately 65–75% of the deaths through cutaneous cancer, with associated high mortality caused by its metastases, which can appear in one third of the cases [1–7]. Thereby, understanding the tumor spread mechanisms and identifying predictive factors for the metastases becomes of crucial importance. However, there are still no adequate biomarkers for the MM metastases prediction [8]. Lately, several matrix metalloproteinases (MMPs) were proposed as predictive factors for the occurrence of MM distant metastases [5, 9]. MMPs represent a complex family of 24 zinc-dependent endopeptidases involved in the proteolysis of the extracellular matrix (ECM), holding therefore key roles in multiple physiological, as well as pathological processes, such as: embryological development; tissue remodeling; wound healing; inflammation; epithelial-to-mesenchymal transformation that enables cell–cell and cell–matrix detachment and therefore allows cellular mobility, migration, and basal membrane perforation; tumor growth, invasion, and spreading; tumor angiogenesis [2, 10–18].

MMPs are classified into collagenases (MMPs 1, 8, 13 and 18), gelatinases (MMPs 2 and 9), stromelysins (MMPs 3 and 10), matrilysins (MMPs 7 and 26), metalloelastases (MMP12), membrane-type MMPs and other MMPs [5, 7, 10, 11, 19].

The process of tumor cell invasion and distant metastatic spreading is dependent on the activity of the MMPs. First, tumor cells suffer an epithelial-to-mesenchymal transition, with cell–cell and cell–matrix detachment. Several MMPs, generated by the tumor cells in response to hypoxic intratumor conditions and increased tissue pressure, start degrading the components of the surrounding extracellular tissue matrix [5, 14].

Also, the expanding tumor cells can penetrate beyond the basement membrane as it is degraded by the MMPs. Therefore, when reaching lymph and blood vessels, the MM cells will enter into circulation, with distant spreading of the tumor cells. The survival and growth of tumor cells at distant metastatic sites will also depend on the activity of the MMPs that will generate a favorable environment [10, 14, 15, 20]. The survival and progression of the MM cells also depends on tumor angiogenesis. Some of the

growth factors with role in tumor angiogenesis are proteolytically activated by various MMPs [5, 15, 18]. An essential mechanism that enables tumor growth and spreading is the tumor immune escape, in the particular inflammatory tumor cell microenvironment. A chronic inflammatory microenvironment is recognized to be a key promoter of tumor development and metastasis, with essential roles for the MMPs as inflammatory modulators. MM cells and other tumor-associated cells can generate MMPs that cleave and degrade cytokines, chemokines, various inflammatory proteins, essential for a normal immune response; also, they can produce growth factors, and even cytokines, express antigens that inhibit the activation of T-cells or induce tolerance from dendritic cells, altering antigen presentation mechanisms [4, 5, 8, 21–23].

MMP1 or interstitial collagenase is an extracellular MMP produced by stromal fibroblasts and tumor cells, belonging to the group of collagenases. MMP1 proteolytically acts on and cleaves components of the ECM, such as native type I, II, III, VII and X fibrillar collagen, enabling tumor progression [5, 7, 12]. MMP1 was found to be overexpressed in several tumors, including MM, where it is associated with tumor invasive phase, metastases, and therefore more aggressive neoplastic phenotypes, being considered a pro-oncogenic protein [5, 10, 16]. Also, MMP1 promotes tumor neoangiogenesis, protects tumor cells from apoptosis, promoting tumor cell survival, growth and chemoresistance [7, 15, 17, 18]. Several synthetic compounds (Marimastat, Rebimastat) have been designed to inhibit MMP1 activity for the treatment of various cancers, including MM [5].

MMP9 or gelatinase B expression and activity is linked to MM invasion and tendency to distant metastases. It is produced by stromal and tumor cells, especially at the tumor border. It digests components of the ECM (gelatin, type IV collagen, elastin, fibrillin, laminin, fibronectin) enabling cell mobility through the disruption of the epithelial integrity, it also activates growth factors [transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α)], promoting tumor growth and angiogenesis [2, 7, 12]. MMP9 will degrade the matrix to create space for tumor cell progression, as well as stimulate tumor neoangiogenesis. Also, as MMP9 is frequently a result of B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) mutations with hyperactivation of mitogen-activated protein kinase (MAPK) pathway, it was proposed as a marker to evaluate the response to the RAF inhibitor drug, Dabrafenib [5]. Some authors reported that simultaneous increase in the heparanase and MMP9 activity is correlated with more advanced tumor stages at the initial diagnostic [24].

MMP11 or stromelysin 3 (belonging to the stromelysin group of MMPs) acts proteolytically on proteoglycans, type IV collagen, gelatin, laminin, fibronectin, therefore intervening in tumor invasion. Stromelysins expression was reported in the primary, as well as in the metastatic MM cells [5].

MMP13 or collagenase-3, from the group of collagenases, is produced by the tumor cells and stroma, fibroblasts, and macrophages, and intervenes in tumor angiogenesis by increasing the generation of VEGF [7, 12] and also it degrades collagen, gelatin, fibrinogen, casein.

Aim

Understanding the putative roles of the MMPs in the mechanisms of metastatic tumor spread and the insufficient knowledge of such processes in MM metastases, the current study aimed to correlate the expression of the MMPs with the evolution of the primitive tumor towards distant metastasis, in order to identify predictors for aggressive behavior and potential therapy targets.

Patients, Materials and Methods

We designed a retrospective cohort study, including 13 patients with metastatic MM diagnosed in our hospital. In all the patients, we made a parallel histological and immunohistochemical (IHC) evaluation of the primary tumor and the metastasis. At least three melanoma IHC stains were used for the diagnosis of all the metastases.

The present study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all the patients.

All the primary cutaneous lesions and metastases were surgically resected. Tissue samples were immersed in 10% neutral buffered formalin, fixed, and then they were processed using an automatic tissue-processor for paraffin-embedding. At least two sections from two different levels were obtained from every paraffin block for Hematoxylin–Eosin (HE) staining; also, additional sections for IHC assays were obtained [S100, human melanoma black 45 (HMB45), melanoma marker, melanocyte inducing transcription factor 1 (MITF1), SRY-box transcription factor 10 (SOX10) – for diagnostic; MMP1, MMP9, MMP11 and MMP13 – for research] (Table 1).

Table 1 – ***Immunohistochemistry data***

Primary antibody	Clone	Host	Pretreatment	Dilution
MMP1	EP1247Y	Rabbit	EDTA	1/400
MMP9	EP1254	Rabbit	EDTA	1/200
MMP11	SN74-08	Rabbit	EDTA	1/200
MMP13	EPR21778	Rabbit	EDTA	1/400

EDTA: Ethylenediaminetetraacetic acid; MMP: Matrix metalloproteinase.

Immunostaining of MMPs was done manually using constant protocols and timings, with antibodies from Abcam. Essentially, at first, the endogenous peroxidase and the unspecific antigenic sites were blocked. Afterwards, the tissue was incubated with primary antibodies for one hour and then thoroughly washed. The signal was amplified with a species-specific detection kit and visualized with 3,3'-Diaminobenzidine (DAB).

The expression of the MMPs was evaluated in the tumor using a three steps scale (0 – negative, 1 – mild positivity and 2 – intense positivity). Also, the percentage of positive tumor cells was evaluated.

Data concerning age, sex, localization of the primary lesion and metastasis, histological and IHC features were statistically analyzed using Microsoft Excel. To evaluate the homogeneity of binary responses grouped as contingency tables, a Fisher's two-tailed test was carried; in all the cases, a p-value <0.05 was considered as statistically significant.

Results

In the present study, we included 13 patients, four

women and nine men, with ages between 33 and 79 years, mean age of 56 years (at the moment of the primary tumor resection) (Figure 1).

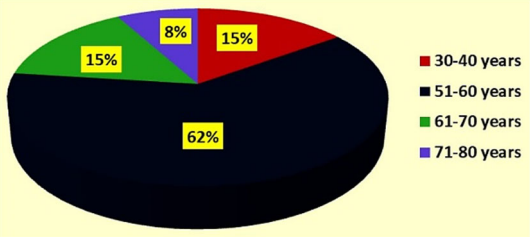


Figure 1 – ***Patient age distribution at the time of the diagnosis.***

They had the primary tumor on the trunk (6/13), lower limbs (5/13), upper limbs (1/13) and on the head (1/13). The metastasis occurred after a mean period of 18.3 months (ranging between 0 months – two patients with lymph node metastasis at the time of the initial diagnosis, and 73 months) (Figure 2). An interesting observation was that in all patients that were free of metastasis at two months after the resection of the initial MM (eight patients), the metastasis appeared after at least one year from the initial diagnosis.

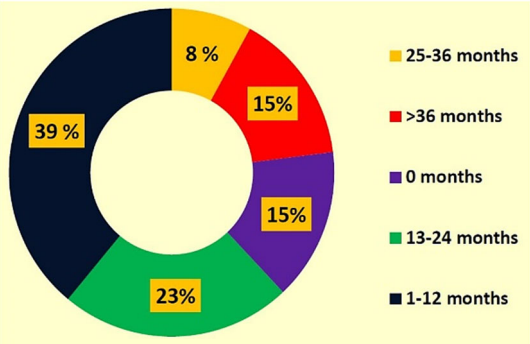


Figure 2 – ***Variable time from the first diagnosis to the occurrence of the metastasis.***

The primary tumors' histological characterization revealed four nodular melanomas, one acral lentiginous melanoma and eight superficial spreading melanoma (SSM) (Figure 3).

All the lesions were thick MM, with Breslow index higher than 1.4 mm (mean Breslow index 4.3 mm). The mitotic index was variable, between 1 and 25 mitoses/mm^2 (mean 6 mitoses/mm^2). Ulceration was absent in just one tumor; all the others being ulcerated lesions. One tumor was pT1b stage, all the other tumors being locally advanced, stage 3 or 4 (Figure 4).

The MMP1 expression in the primary tumor was identified in five cases, with mild intensity in four cases and intense positivity in one case (Figure 5, A and B). Also, the percentage of MMP1-positive tumor cells was low (between 10% and 40% of the cells, with a mean value of 20%). From the metastasis group, five patients were also positive, but only four patients were the ones with MMP1-positive primary tumor. The case with intense positivity for MMP1 in the primary tumor had a completely negative metastasis, while a case with negative initial tumor had intense positivity in 90% of metastasis tumor cells.

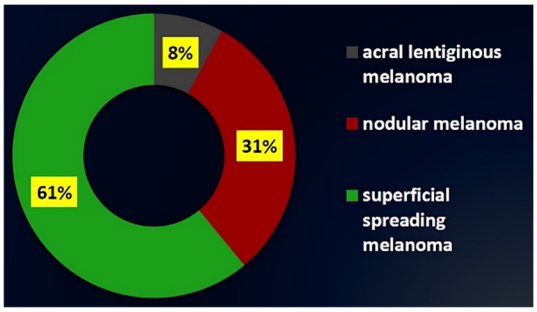


Figure 3 – ***Microscopic features of the primary tumor.***

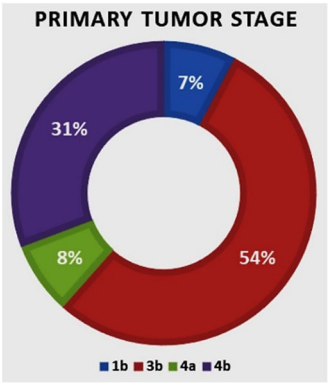


Figure 4 – ***The pathological stage of the primary tumor.***

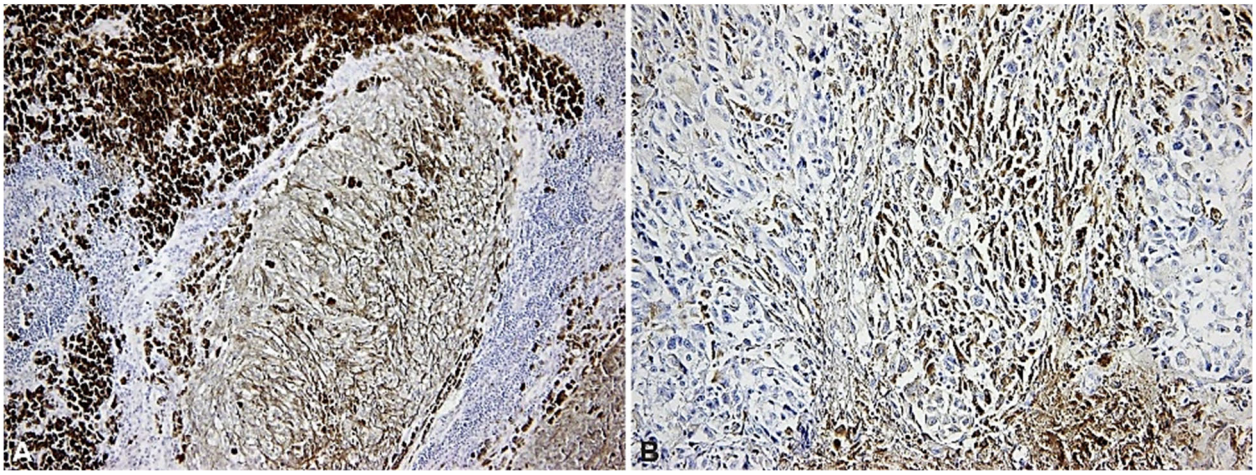


Figure 5 – ***Mild positivity for MMP1 in a primitive MM (40% of the tumor cells – A) and its metastasis (50% of the tumor cells – B). Note the significant pigmentation with melanin of the primitive tumor (A – upper corner). Immunostaining for MMP1: (A and B) ×100. MM: Malignant melanoma; MMP1: Matrix metalloproteinase 1.***

The MMP1 staining intensity in the metastatic cells was mild in four cases (the same that had mild positivity in the primary tumor as well) (Figure 6).

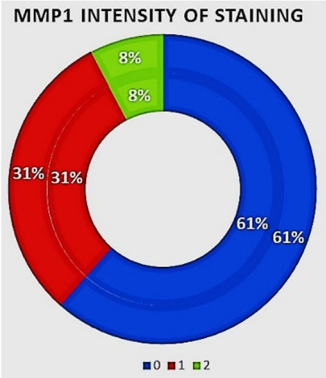


Figure 6 – ***MMP1 expression in the primary MM (inner circle) and its metastasis (outer circle) (0 – negative; 1 – mild positivity; 2 – intense positivity). MM: Malignant melanoma; MMP1: Matrix metalloproteinase 1.***

In all the four cases that showed positivity for MMP1 in both lesions, the percentage of metastatic positive cells was equal or higher than the one in the initial tumor. The MMP1-positive metastatic cells percentage ranged from 10% to 90%, with a mean value of 58% (Figure 7).

Patients with early metastasis (in the first two months from the initial diagnosis) had a high expression of MMP1 in the metastatic cells, 40% *vs.* 10% in patients that were diagnosed with the metastasis later.

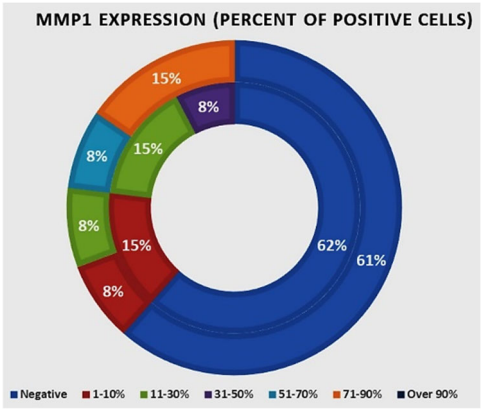


Figure 7 – ***MMP1 expression in the primary MM (inner circle) and its metastasis (outer circle). MM: Malignant melanoma; MMP1: Matrix metalloproteinase 1.***

MMP9 was positive in 12 cases, both in the primary tumor and metastasis. One case was completely negative for MMP9 in the primary tumor and metastasis as well (it was also negative for all the tested MMPs in both lesions, an elderly female patient with SSM and dermic metastasis after 22 months from the initial diagnosis) (Figure 8, A and B).

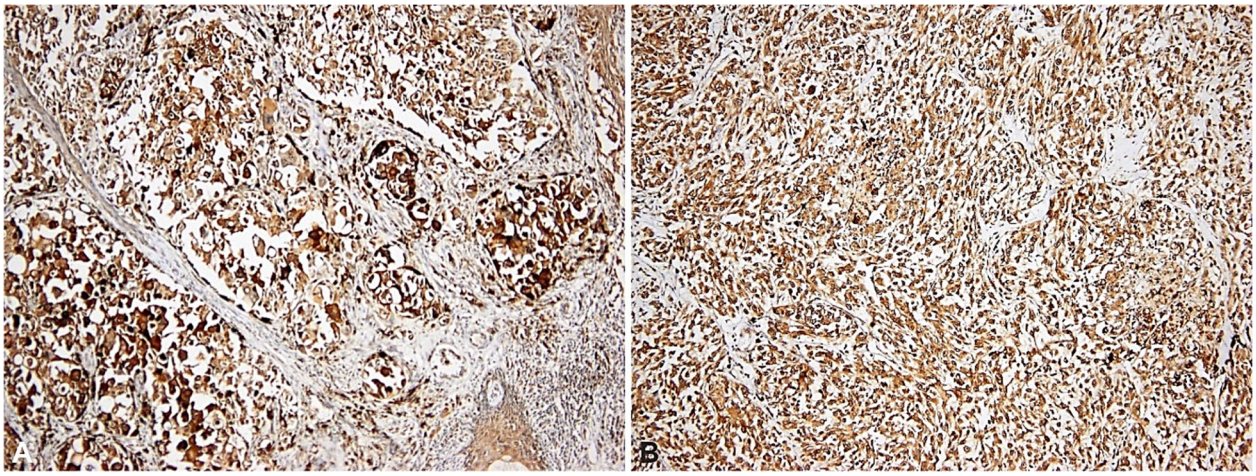


Figure 8 – ***Mild intensity for MMP9 in a primitive MM (70% of tumor cells – A) and its lymph node metastasis (100% of tumor cells – B). Immunostaining for MMP9: (A and B) ×100. MM: Malignant melanoma; MMP9: Matrix metalloproteinase 9.***

In the primary tumor, the staining intensity was high in four cases and mild in eight cases, while in the metastasis it was high in eight cases and mild in four cases. The percentage of positive cells was higher in the metastasis than in the primary tumor (ranging from 5% to 100%, with a mean value of 68% in the primary tumor, *vs.* 10% to 100% range, with a mean value of 72% in the metastasis) (Figure 9).

In 11 cases, the percentage of MMP9-positive tumor cells was at least equal or higher in the metastasis than in the primary tumor. Also, the MMP9 staining intensity was at least equal or higher in the metastatic cells than in the primary tumor cells (Figure 10).

Early metastases were richer in MMP9-positive cells than the later ones (80% *vs.* 50%), regardless of the positivity of the primitive tumor.

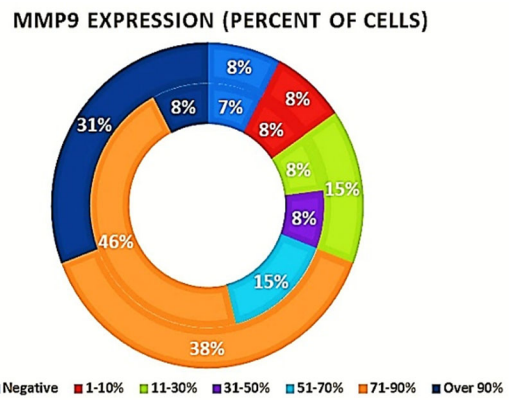


Figure 9 – ***MMP9 expression in the primary MM (inner circle) and its metastasis (outer circle). MM: Malignant melanoma; MMP9: Matrix metalloproteinase 9.***

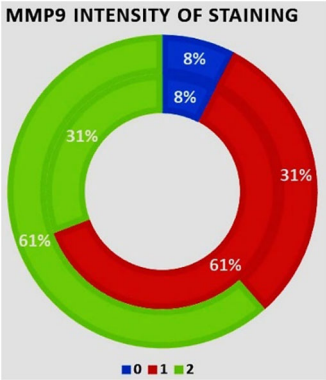


Figure 10 – ***MMP9 expression in the primary MM (inner circle) and its metastasis (outer circle) (0 – negative; 1 – mild positivity; 2 – intense positivity). MM: Malignant melanoma; MMP9: Matrix metalloproteinase 9.***

MMP11 was expressed in 12 primary tumors and 11 metastases (the case with negative primary tumor and another case with 20% positivity in the primary tumor) (Figure 11, A and B).

The percentage of positive cells ranged between 5% and 70% in the primary tumor (mean value 30%), and between 20% and 70% (mean value 36%) in the metastasis (Figure 12).

No correlation between the percentage of positive cells and the MMP11 staining intensity between the primary tumor and its metastasis was observed. Also, no correlation between the precocity of the metastasis and the percentage or intensity of the MMP11 staining was recorded.

MMP13 was also expressed in 12 cases, both in the primary and secondary tumors (Figure 13, A and B).

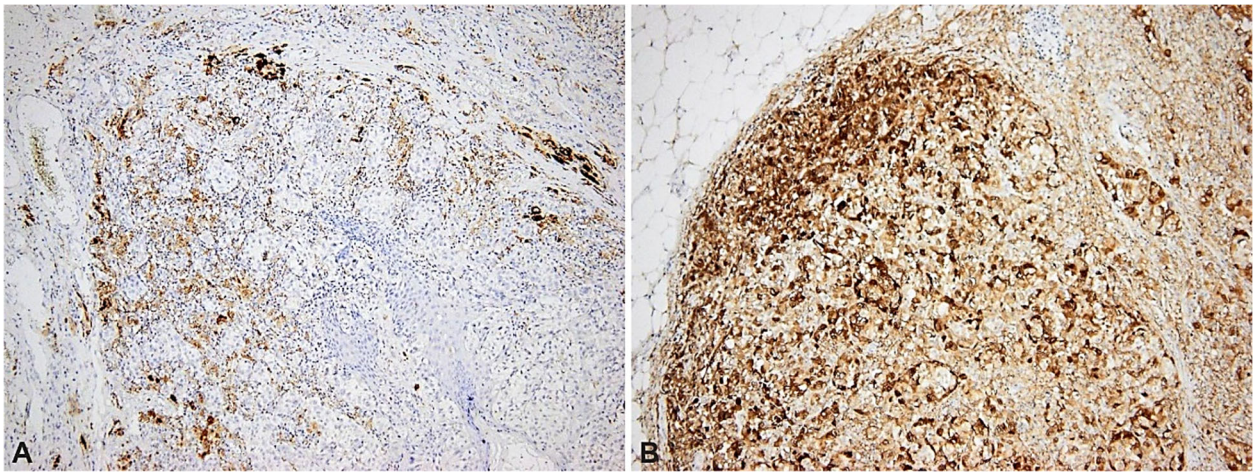
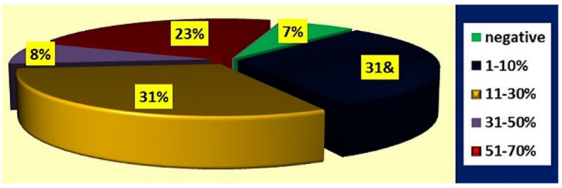


Figure 11 – ***Intense positivity for MMP11 in a primary MM (10% of cells – A) and its metastasis (70% of cells – B). Although the primitive tumor has a minor MMP11-positive component, the metastasis expressed MMP1 in the majority of the cells. Immunostaining for MMP11: (A) ×40; (B) ×100. MM: Malignant melanoma; MMP11: Matrix metalloproteinase 11.***

Figure 12 – ***MMP11 expression in the primary MM (inner circle) and its metastasis (outer circle). MM: Malignant melanoma; MMP11: Matrix metalloproteinase 11.***



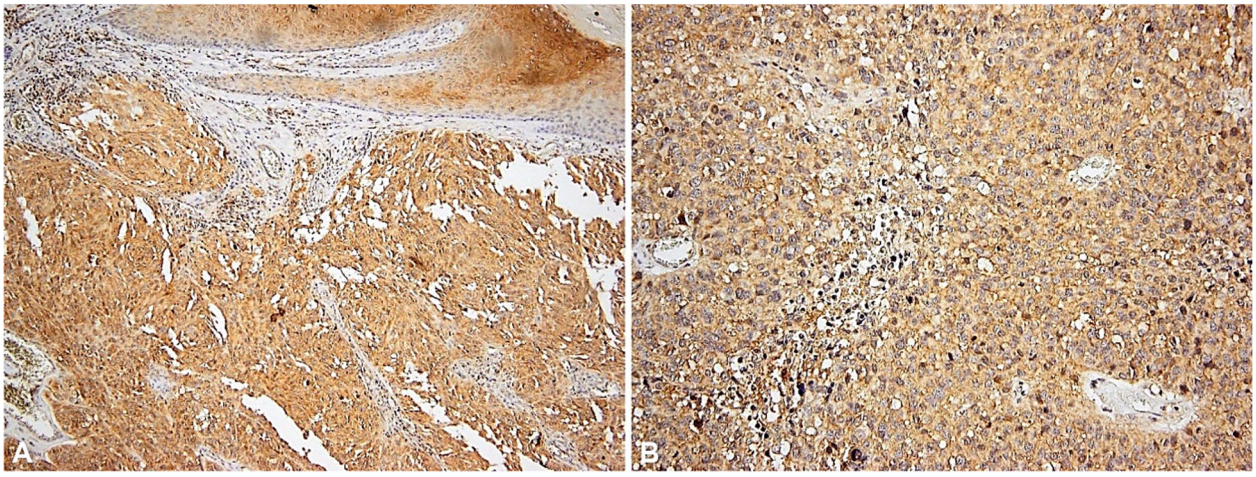


Figure 13 – ***Mild positivity for MMP13 in a primary MM (90% – A) and its metastasis (90% – B). Immunostaining for MMP13: (A) ×100; (B) ×200. MM: Malignant melanoma; MMP11: Matrix metalloproteinase 13.***

The percentage of positive cells varied between 10% and 100% (with a mean of 50%) in the primary tumor, while in the metastases it ranged from 50% to 100% (with a mean of 86%) (Figure 14). The staining intensity was

mostly mild in the primary tumors (10 cases) and mostly high in the metastases (eight cases).

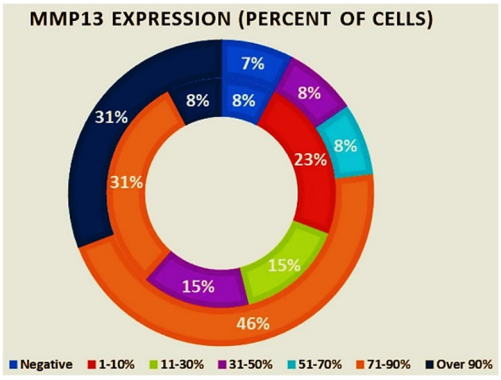


Figure 14 – ***MMP13 expression in the primary MM (inner circle) and its metastasis (outer circle). MM: Malignant melanoma; MMP13: Matrix metalloproteinase 13.***

In all the metastases, the percentage of positive cells and MMP13 staining intensity was higher (or at least equal) than in their primitive tumors.

Also, MMP13 was highly expressed in the early metastases, 90%, *vs.* 60% in the late metastases.

Discussions

Several studies have reported a particular significance for the expression levels of MMPs 1, 2, 3, 9, 14 and 15 in MM [2, 13, 20, 25, 26]. An increased level of activity, higher aggressiveness, and a potential predictive role for the occurrence of distant metastases was seen especially for MMPs 2 and 9 [13]. However, later, the results have shown that only some MMPs hold a pro-tumor function, while others may be actually protective against the development of cancer, such as against MM [5].

As MM metastases can occur in a high percentage of cases and hold a very unfortunate prognosis for MM patients, the time until the diagnostic of the first metastasis is a very important indicator of evolution [3, 27–29]. Correlation of the MMPs expression with this indicator reveals some aspects with high significance in the patients' management.

The statistical analysis of the obtained data revealed that the time from the primary tumor to the metastasis correlates with the percentage of MMP1 (p=0.0035) and MMP9 (p=0.0019) positive cells found in the metastatic lesions. Practically, the metastases rich in MMP1- and MMP9-positive cells occurred earlier than metastases with low level of positive cells. This observation correlates with data from literature that show a higher aggressiveness for MMP1- and MMP9-positive clones of malignant melanocytes [5, 10, 16].

The mean period until metastasis was shorter for tumors expressing MMP1 than the ones without MMP1 expression (12.14 months *vs.* 25.5, p=0.0267). Also, the metastasis that expressed MMP1 occurred significantly earlier than the ones negative for MMP1 (21.9 months *vs.* 12.6 months, p=0.0431). The percentage of MMP1-positive tumor cells in the primary tumor was not significantly correlated with the risk of rapid evolution towards metastasis, indicating the fact that there are some tumor cells groups that metastasize quicker, no matter of their prevalence in the tumor mass and the simple fact that a primary MM has MMP1-positive cells is a risk factor for early metastasis.

Practically, using their capacity to synthetize MMP1 and MMP9, melanoma cells affect matrix components, facilitating their migration and invasion. Also, MMP1 acts as an activator for various growth factors (as TGF-β) which increase the capacity of invasion and distant spread [30]. Recent studies proposed MMP1 and MMP9 as biomarkers for surveillance of MM evolution, as well as therapeutic targets in uveal melanoma treatment [31], estimating that knockdown of MMP1 could inhibit disease progression, as it was demonstrated in colorectal carcinoma [32].

Since MMP1 promotes tumor neoangiogenesis, the expression and activation of several vascular growth factors, including VEGF, activation of the VEGF pathway, endothelial cells proliferation, and by increasing the expression level of protease-activated receptor-1 (PAR-1) [7, 18], further studies are needed to correlate expression of MMP1, and these vascular factors involved in MM progression and metastasis.

MMP9 acts as aggressiveness factor in MM, probably using MAPK signaling pathway, frequently associated with *BRAF* mutations [13, 33]. These data are a significant argument for further use of MMP9 as tissue and serum biomarker to predict the evolution towards metastasis and to evaluate the efficiency of therapeutic molecules.

Although overexpressed in MM and their metastasis, MMP11 failed, in this study, to correlate with MM progression, confirming other studies that found that MMP11 is related to progression in non-melanoma skin cancers [34]. Probably MMP11 is involved in MM only in tumor regression, as revealed by previous studies [10, 25].

MMP13 expression in the tumor and its metastasis was significantly linked with the time until the metastasis' occurrence. Thus, taking a cut-off value of 20% of the tumor cells for the expression of MMP13 in the primary tumor, patients with a low expression of MMP13 had a significantly shorter free-of-metastasis survival than the patients with high expression of MMP13 in the primary tumor cells (average 11 months *vs.* 23 months, p=0.0357). Also, the patients that had all the metastatic tumor cells positive for MMP13 had a significantly shorter period of evolution towards metastasis than the patients with lower expression of MMP13 in the metastatic cells (average 25 months *vs.* 3.75 months, p=0.0084). These data are confirming some *in vitro* studies that showed that MMP13 mediates cell cycle progression in melanoma cell lines [35, 36]. Meierjohann *et al.* [35] demonstrated that knockdown of MMP13 synthesis by melanoma cells is correlated with decreased proliferation. Since MMP13 inhibitors are already available and used in trials for other diseases, this is promising information, in order to identify new therapeutic agents to prevent MM proliferation and progression.

Conclusions

Although involving a small cohort, this study identified interesting correlations between the MMPs' expression in the primary MM and its metastasis. This data is a step forward on the way to identify novel biomarkers of progression as well as novel therapeutic targets to treat metastatic MM. This study addresses a significant indicator of patients' evolution: the time from the first diagnosis until the first metastasis and has found some interesting correlations

between MMPs expression and this indicator. Understanding the mechanisms involved in the progression towards metastasis in MM is important to find key-points in which we can intervene with molecules to inhibit or at least delay the spread of the primitive tumor. This study emphasizes the roles of MMP1, MMP9 and MMP13 in the process of MM metastasis and the opportunity to use them as therapeutic targets and surveillance molecules.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author
Angela Mădălina Lazar, Assistant Professor, MD, PhD, Department of General Surgery, Colentina Clinical Hospital, 19–21 Ştefan cel Mare Street, Sector 2, 020125 Bucharest, Romania; Department of Functional Sciences, Carol Davila University of Medicine and Pharmacy, 8 Eroilor Sanitari Avenue, Sector 5, 050474 Bucharest, Romania; Phone +4021–317 32 45, e-mail: angelalazar.2008@yahoo.com

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