Immunohistochemical expression of PRAME in uveal melanoma: a clinico-pathologic and immunohistochemical studyon a series of 85 cases

Giuseppe Broggi[a], Maria Failla[a], Andrea Russo[b], Antonio Longo[b], Andrea Palicelli[c], Magda Zanelli[c], Claudia Lombardo[d], Carla Loreto[d], Francesco Merolla[e], Rosa Maria Di Crescenzo[e], Gennaro Ilardi[e], Silvia Varricchio[f], Stefania Staibano[f], Rosario Caltabiano[a]

[a]*Department of Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Anatomic Pathology, University of Catania, 95123 Catania, Italy*

[b]*Department of Ophthalmology, University of Catania, 95123 Catania, Italy*

[c]*Pathology Unit, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy*

[d]*Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Human Anatomy, University of Catania, 95123 Catania, Italy*

[e]*Department of Medicine and Health Sciences "V. Tiberio", University of Molise, 86100 Campobasso, Italy*

[f]*Department of Advanced Biomedical Sciences, Pathology Section, University of Naples "Federico II", 80131 Naples, Italy*

Background

Uveal melanoma (UM) is, despite being a rare entity, the most frequent primary intraocular malignancy of adults and although numerous clinical and histopathological features of UMs have been studied in order to predict the patient's relative risk of developing metastasis, none of them individually or in combination has proven to be decisive for identifying which patients will develop metastasis.

PReferentially expressed Antigen in Melanoma (PRAME) is a promising protein for this objective, since several studies suggested that high PRAME expression could be associated with poor prognosis in terms of increased risk of metastases and shorter disease-free and overall survival in solid tumors. Regarding melanocytic pathology, PRAME immunohistochemical expression is a valuable tool in differential diagnosis between nevi and melanoma, being significantly more expressed in melanoma rather than nevi.

Objectives

In the present study we investigated the immunohistochemical expression of PRAME on a series of 85 primary UMs and correlated it with clinico-pathologic and prognostic data of patients from our cohort in order to assess whether PRAME could be considered an useful prognostic tool to early identify cases with high risk of metastases.

Methods

We performed a retrospective study on histologic specimens from 85 primary UMs, surgically enucleated from October 2009 to October 2019, and collected the following clinical data: (i) largest tumor diameter and anatomic location, (ii) metastatic spread, and assessed PRAME expression through immunohistochemistry. It was considered positive if brown chromogen was observed, at least focally, within the tumor cell nuclei.

	PRAME expression	
	present	absent
Metastasis free (n = 45)	14 (31.1 %)	31 (68.9 %)
Metastasis (n = 40)	23 (57.5 %)	17 (42.5 %)
p (Fisher's exact test)	0.017	

Table 1
Number of uveal melanoma (with and without metastasis) with and without PRAME expression.

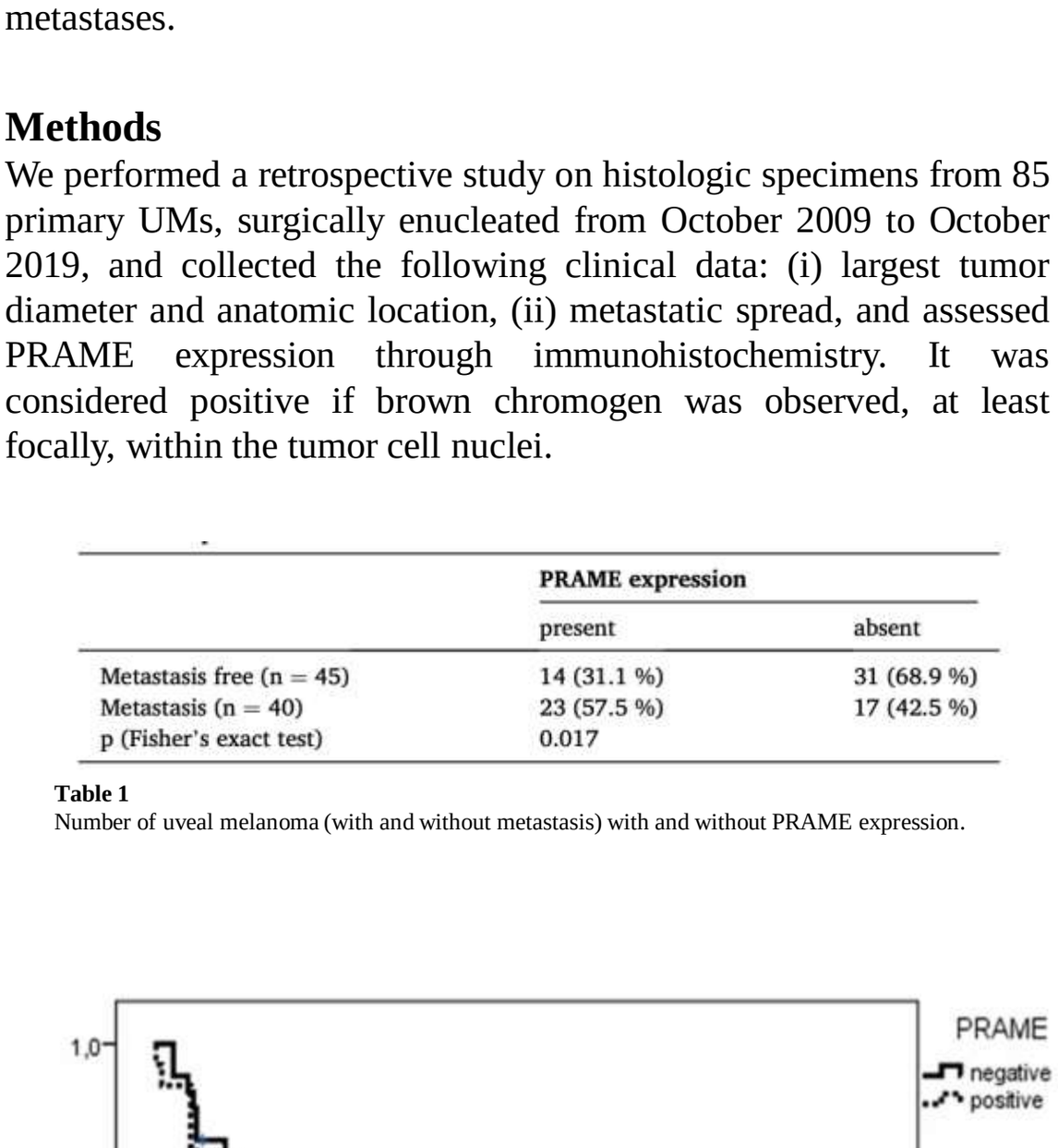

Fig. 2. Kaplan-Meier survival curve. Patients affected by UM showing PRAME immunoreactivity had lower metastasis-free survival times than those with no expression of this protein.

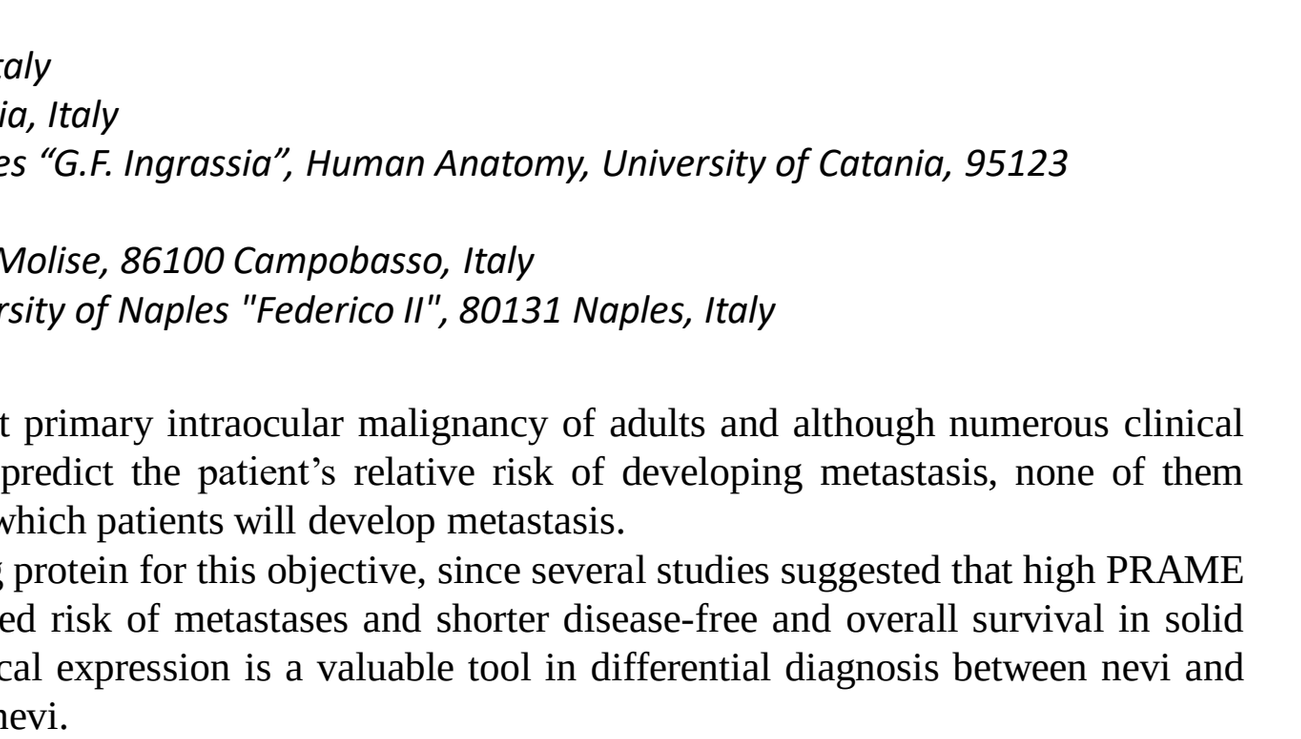

Fig. 1. Diffuse and strong PRAME immunohistochemical expression. A, B) Two examples of metastasizing uveal melanomas exhibiting diffuse and strong PRAME immunoreactivity (A, B: immunoperoxidase; original magnifications 300x).

Results

Of the 85 patients (44 males and 41 females with a median age of 67 years; age range 29–85), forty patients showed liver metastases.

The cohort of 45 non-metastasizing cases included 25 males and 20 females with ages ranging from 19 to 84 months (median: 64 years). Among the 40 metastasizing UMs, 19 were males and 21 were females, with ages ranging from 50 to 85 years (median: 71 years). As a result of disease progression, 25 out of the 40 metastatic patients died during the follow-up period.

Among the 45 primary non metastatic UMs, 14/45 cases (31.1 %) showed a PRAME expression, while the other 31 UMs did not show PRAME expression (68.9 %). In the 40 primary metastatic UMs 23/39 cases (57.5 %) had at least focal PRAME expression, while no PRAME expression was found in the remaining 17/40 UMs (42.5 %).

We found positive PRAME expression, at least focally within the tumor cell nuclei, in 37 cases. PRAME positive cases showed a significant risk of metastasis (57.5 %) with respect to PRAME negative cases (31.1 %).

Conclusions

The topic of finding an immunohistochemical marker that could better stratify risk in UM patients is currently being investigated thoroughly, since the potential identification of a high-risk group of patients could improve their management by increasing the frequency of controls to identify cases with liver metastases earlier that could be safely surgically excised, thus improving overall survival.

PRAME is a tumor-associated antigen that has currently sparked the interest of many Authors, and its expression and role is being investigated in different neoplasms, including UM, in which appears to be useful in distinguishing a subgroup of UMs that may metastasize.

This hypothesis was confirmed by our study which reported a significant association between PRAME expression in 85 UM patients and risk of metastasis, and a worse overall survival and disease-specific survival.

In conclusion, we suggest using PRAME as an easily detectable prognostic marker in primary UMs to improve patient stratification by risk of metastasis, and therefore as a guide for monitoring and treatment.

Additional perspectives of our study include the possibility of investigating the role of PRAME as target for treatment in metastatic UM.

References

[1] F. Spagnolo, G. Caltabiano, P. Queirolo, Uveal melanoma, Cancer Treat. Rev. 38 (2012) 549–553, https://doi.org/10.1016/j.ctrv.2012.01.002.

[2] G. Broggi, G. Musumeci, L. Puzzo, A. Russo, M. Reibaldi, M. Ragusa, A. Longo, R. Caltabiano, Immunohistochemical expression of ABCB5 as a potential prognostic factor in uveal melanoma, Appl. Sci. 9 (2019) 1316, https://doi.org/10.3390/ app9071316.