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Immunohistochemical expression of PRAME is a marker of poor prognosis in uveal melanoma: A clinico-pathologic and immunohistochemical study on a series of 85 cases

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ABSTRACT

PReferentially expressed Antigen in Melanoma (PRAME) is a cancer testis antigen, first isolated in tumor-reactive T-cell clones from a metastatic melanoma patient. It has been widely studied in skin pathology as an immunohistochemical marker capable of distinguishing between benign nevi and malignant melanomas. PRAME has been found to be also expressed in non-melanocytic tumors, including lung, breast, kidney and ovarian cancer. However, less is known about the diagnostic and/or prognostic role of this protein in uveal melanoma (UM); few studies have reported that PRAME expression seems to give to UM patients an additional metastatic risk beyond the other already-known prognostic parameters. In the present retrospective study, we aimed to correlate PRAME immunoreactivity to other clinico-pathologic features and follow-up data on a large series of 85 cases (45 non-metastasizing and 40 metastasizing tumors) of primary UM. A statistically significant correlation was found between PRAME expression and higher metastatic risk and lower metastasis-free survival. We propose to include PRAME in the immunohistochemical panel of UM as an easily usable marker capable of predicting higher metastatic risk and stratifying patients' outcome.

1. Introduction

Uveal melanoma (UM) is the most frequent primary intraocular malignancy of adults and primarily arises from melanocytes within the choroid, the ciliary body and the iris [1–3]. While over the years 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 [4,5].

Certain chromosomal aberrations (most notably chromosome 3 monosomy) and the gene expression profile (GEP) (Castle Biosciences, Friendswood, TX) of UM cells have recently been shown to be useful for classifying an individual UM patient's metastatic risk [6,7]. GEP class 1 is divided into two subsets: class 1 A tumors carry low metastatic risk; class 1B tumors have intermediate risk; while class 2 tumors have high risk [4].

Another interesting topic that many researchers have focused on is the development and discovery of immunohistochemical biomarkers capable of predicting metastatic risk [8].

PReferentially expressed Antigen in Melanoma (PRAME) is a tumor-associated antigen that was first identified through the analysis of the specificity of tumor-reactive T-cell clones derived from a patient with metastatic cutaneous melanoma [9,10]. Subsequently, it was found to be expressed in somatic unaffected tissues such as testis, ovary, placenta,

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adrenals and endometrium, while in the oncological field PRAME expression has been reported in cutaneous melanoma, UM and other nonmelanocytic malignancies including non-small cell lung cancer, breast carcinoma, renal cell carcinoma, ovarian carcinoma, leukemia, synovial sarcoma and myxoid liposarcoma [10–13].

Several studies showed 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, whereas it has been found to predict a more favorable outcome in acute myeloid and lymphoblastic leukemia [11]. PRAME expression in UM was first recognized to confer an additional metastatic risk beyond GEP status and it is now part of a 12-gene array prognostic assay for uveal melanoma [9,10,14].

Because of its expression profile, PRAME is a member of the family of cancer testis antigens (CTA), and an attractive target for immunotherapy [11]. Since PRAME tumor expression has been shown to elicit spontaneous humoral and cellular immune responses, and PRAME-based vaccines and adoptive T-cell therapies have shown a favorable safety profile and efficient induction of potent immune responses in tumors, a number of clinical trials are underway trying to exploit PRAME for cancer treatment [9–11,15,16].

There is clinical interest in UM as a potential biomarker for diagnosis and prognosis, as well as a potential target for treatment, 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.

2. Materials and methods

We performed a retrospective study on histologic specimens from 85 primary UMs, surgically enucleated at the Ophthalmologic Clinics of the University of Catania and the University of Naples "Federico II" from October 2009 to October 2019. The corresponding clinico-pathologic data were retrieved from the original pathologic reports. For all the patients from our cohort, the enucleation was the only therapeutic option, as they were not eligible for plaque brachytherapy or proton-beam radiotherapy. From each case, representative paraffin-blocks were retrieved from the Pathology archives of the Department G.F. Ingrassia, University of Catania, and from the Department of Advanced Biomedical Sciences, University of Naples "Federico II". Cases in which paraffin blocks containing the tumor could not be used to obtain additional slides for immunohistochemical evaluation, representative tumor tissue was not present, the tumor was totally necrotic or had been treated previously, were excluded from the study. Tissue samples were evaluated separately by three pathologists (G.B., M.F. and R.C.), with no information on the clinical data of the patients.

Of the 85 patients that met the inclusion criteria and were included in the study, 44 were males and 41 were females (median age: 67 years; age range 29–85). The study included 40 metastasizing UMs and 45 non-metastasizing UMs. We collected the following clinical data: (i) largest tumor diameter and anatomic location, both evaluated by ophthalmoscopy and A- and B-scan ultrasound exams; (ii) metastatic spread, detected by liver ultrasound exams and whole body computed tomography (WBCT).

PRAME expression status can be detected using reverse-transcription polymerase chain reaction (RT-PCR) or immunohistochemistry (IHC) [17].

We decided to assess PRAME expression through immunohistochemistry since PRAME RT-PCR and IHC provide concordant results in most cases, and, furthermore, IHC reveals focal PRAME expression in subsets of tumor cells consistent with tumor heterogeneity [17–19].

PRAME immunohistochemical staining was considered positive if brown chromogen was observed, at least focally, within the tumor cell nuclei.

2.1. Statistical analysis

The rates of present and absent PRAME expression in melanoma of patients with and without metastasis were non parametrically compared using the chi-square test. Agreement among observers was tested by Cohen's K coefficient. Univariate and multivariate analyses, based on a Cox proportional hazards regression model (time free from metastasis as outcome), were performed; gender, age, melanoma location (choroid or ciliary body), temporal or nasal location, cells type (epithelioid, spindle cells or mixed), echography parameters (height, greatest diameter), and PRAME expression (present and absent) were all included in this model. If a predictor had a P value < 0.15 (cut off) in the univariate analysis, it was included in the multivariate one. Survival analysis according to PRAME expression (present/absent) was performed using the Kaplan-Meyer test; survival rates were compared by the log-rank (Mantel-Cox) test.

P values <0.05 were considered statistically significant.

3. Results

3.1. Clinico-pathologic features of uveal melanomas

Of the 85 patients (44 males and 41 females with a median age of 67 years; age range 29–85), an exclusive choroidal localization and a simultaneous involvement of the choroid and ciliary bodies were found in 64 and 21 UMs, respectively. Three cases showed extra-scleral invasion. Histologically, 20 cases exhibited an epithelioid morphology, 25 a spindle cell morphology, while 40 cases were diagnosed as mixed-type. Forty patients showed liver metastases. Follow-up times ranged from 8 to 138 months (median value: 58 months).

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.

Supplementary Table 1 and 2 sum up all clinico-pathologic features of the cases from our series.

No significant differences were observed in median age, melanoma anatomic location (choroid or choroid and ciliary body), melanoma thickness, histologic subtype, extra-scleral extension and pathologic T stage between metastasizing and non-metastasizing cases; patients with metastatic spread exhibited tumors with greater largest median diameter (15.4 mm versus 12.4 mm, $p = 0.009$), PRAME expression ($p < 0.001$) and shorter median metastasis-free survival (25 months versus 73 months, $p < 0.001$) (Supplementary Table 3).

3.2. PRAME immunohistochemical expression in uveal melanomas

In the overall cohort of patients included in the study ($n = 85$) PRAME expression was present (positive) in 37 and absent (negative) in 48 UMs.

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 (Fig. 1A, B), while no PRAME expression was found in the remaining 17/40 UMs (42.5 %) (Fisher's exact test, $p = 0.017$, Table 1).

Factors related to the presence of metastasis at univariate analysis on a Cox proportional hazards regression model were: age ($p = 0.005$), diameter ($p = 0.046$), epithelioid cell type ($p = 0.008$), pT stage ($p = 0.012$), and PRAME immunoreactivity ($p = 0.007$).

At multivariate analysis epithelioid cell type ($p = 0.045$), pT stage ($p = 0.032$), and PRAME immunoexpression ($p = 0.039$) were significant.

No correlation was found between histological type and PRAME

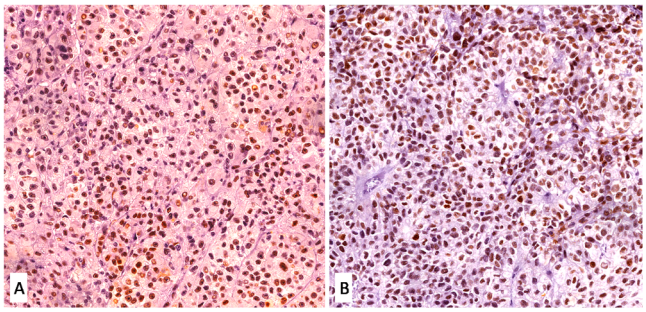

Fig. 1. Diffuse and strong PRAME immunohistochemical expression. A, B) Two examples of metastasizing uveal melanomas exhibiting diffuse and strong PRAME immunoreactivity (A, B: immunoperoxidase; original magnifications 300x).

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

	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	

expression (Spearman's rho p = 0.720).

Fig. 2 shows the results of Kaplan–Meier survival analyses in patients with UM with present and absent PRAME immunoexpression. The mean survival time free from metastasis (SE, with 95 % CI) estimated were 138.8 (12.1) (CI: 115.1–162.5) and 60.6 (8.0) (CI: 45.0–76.3) months, respectively. The log-rank test showed a significant difference (p = 0.005) between the two groups.

4. Discussion

Uveal melanoma (UM) is considered a rare neoplasm, which differs from their more common cutaneous melanoma relative in risk factors, primary treatment, anatomic spread, molecular changes, and responses to systemic therapy [20]. The most common location for UMs is the choroid (90 %), followed by the ciliary body (6 %) and then iris (4 %) [21]. The most important risk factors for UM include fair skin, light eye color, inability to tan, ocular or oculodermal melanocytosis, cutaneous or iris or choroidal nevus, and germline BRCA1- associated protein 1 mutation [22].

At the moment, the most diffused first-line treatment options for UM are radiation therapy, and enucleation. Though these therapies generally achieve satisfactory local disease control, the long-term survival rate for patients with UM remains poor, with the risk for developing liver metastasis [22].

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 [23].

PRAME is a promising protein for this objective and also an attractive target for immunotherapy, its role being investigated in a number of solid and hematologic neoplasms [24]. It was first reported as a cell

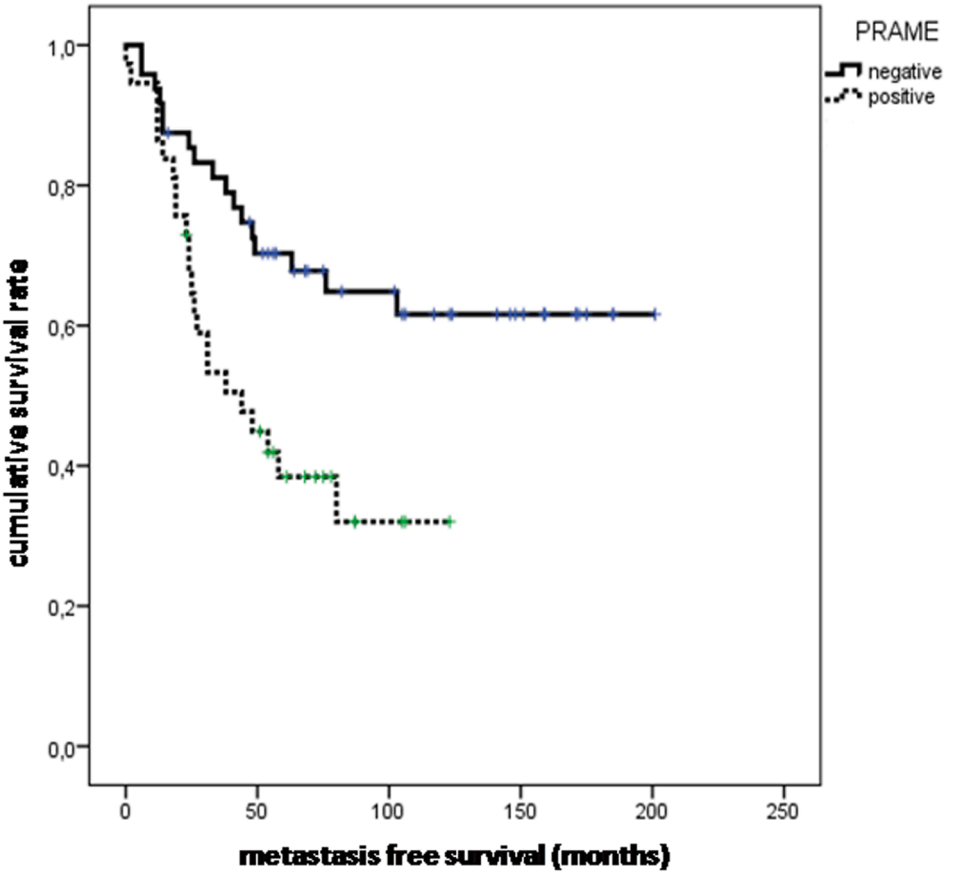

Fig. 2. Kaplan-Meier survival curve. Patients affected by UM showing PRAME immunoreactivity had lower metastasis-free survival times than those with no expression of this protein.

membrane protein antigen highly expressed by metastatic cutaneous melanoma [25]. PRAME encodes the human leucocyte antigen, (HLA)-A24, and is localized on chromosome 22 (22q11.22). It belongs to the CTA gene family and encodes antigen peptides recognized by T-Lymphocytes [9]. The PRAME gene has been reported hypermethylated in normal tissues, but hypomethylated in the majority of malignant cells. In the literature, low expression of PRAME has been observed in normal testicular, ovarian, endometrial and adrenal tissues, but it was over-expressed in a number of human malignancies such as head and neck squamous cell carcinomas, non-small cell lung cancers, and breast cancer [10–13].

Regarding melanocytic pathology, immunohistochemical expression of PRAME is useful in distinguishing nodal nevi from metastatic melanoma [24]. Furthermore, regarding cutaneous melanocytic lesions, PRAME immunohistochemical expression is a valuable tool in differential diagnosis between nevi and melanoma, being significantly more expressed in melanoma rather than nevi [26]. In UM it plays a different role considering that it appears to be useful in distinguishing a subgroup of UMs that may metastasize.

This hypothesis was confirmed by our study that reported a significant association between PRAME expression in 85 UM patients and risk of metastasis, and a worse overall survival and disease-specific survival. We found negative PRAME nuclear expression in 48 cases with no UM tumor cells expressing PRAME by IHC. 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 %).

These findings are in agreement with those highlighted in studies by different authors who identified PRAME as an independent risk factor for increased metastatic risk in GEP class 1 or class 2 tumors [8,24,27].

Other studies reported that PRAME expression in primary UMs was associated with a poorer disease-specific survival [24,28]. Rusakevich et al. aimed at evaluating the association between clinical and ultrasound features of UM and PRAME, given its role as a biomarker for metastatic mortality; they found a correlation between PRAME positivity with the largest basal diameter (LBD) of the tumor [29].

Nevertheless, Cai et al. suggest that in UM, molecular prognostic testing using GEP and PRAME individually provided prognostic accuracy that was superior to TNM staging in predicting a patient's risk of developing metastasis [30]. Moreover, they claim that combining GEP with PRAME could create an even more efficient and simplified 3-category molecular prognostic model. These findings continue to support the superior prognostic accuracy of these molecular biomarkers over anatomic features [30].

Another future perspective is provided by Gezgin et al. who also demonstrated that the high-affinity, PRAME-specific T-cells are able to efficiently recognize PRAME-positive UM cell lines and therefore suggest treating UM metastases that express PRAME with PRAME-TCR gene therapy [28].

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.

5. Conclusions

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.

Our study confirms the findings that PRAME expression is an independent risk factor for increased metastatic risk in GEP class 1 or class 2 UMs, and it correlates with a poorer disease-specific survival.

The main limitation of our study is the relatively small sample size, and further multi-institutional studies on larger series are required to validate our findings and to better clarify the complex interaction between PRAME expression and the risk of liver metastasis.

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

Compliance with ethical standards

The study complied with the Ethical Principles for Medical Research Involving Human Subjects according to the World Medical Association Declaration of Helsinki; the non-interventional, retrospective nature of our study did not require any informed consent, even if a written informed consent had been obtained from the patient before surgical procedures. The clinical information had been retrieved from the patients' medical records and pathology reports. Patients' initials or other.

personal identifiers did not appear in any images. Finally, all samples were anonymized before histology, immunohistochemistry and molecular analysis; therefore, no further ethical approval was necessary to perform the study.

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CRediT authorship contribution statement

Giuseppe Broggi: Conceptualization, Investigation, Writing - original draft. **Maria Failla**: Methodology, Writing – original draft. **Andrea Russo**: Methodology, Resources. **Antonio Longo**: Formal analysis, Resources, Data Curation. **Andrea Palicelli**: Resources. **Magda Zanelli**: Resources. **Claudia Lombardo**: Resources. **Carla Loreto**: Resources. **Francesco Merolla**: Resources. **Rosa Maria Di Crescenzo**: Resources. **Gennaro Ilardi**: Resources. **Silvia Varricchio**: Resources. **Stefania Staibano**: Resources, Data Curation. **Rosario Caltabiano**: Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prp.2023.154543.

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