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Original Contribution

Metastases from uveal melanoma may lack S100 expression: A clinico-pathologic and immunohistochemical study with emphasis on potential causes and diagnostic implications

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ABSTRACT

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with a high mortality rate due to metastasis, primarily to the liver. The differential diagnosis of metastatic UM, particularly in distinguishing it from cutaneous melanoma (CM), can be challenging due to overlapping histopathological features. This study investigates the immunohistochemical expression of S100 in a cohort of 41 cases, including 13 metastatic UMs, 18 metastatic CMs, and 10 primary UMs. Our results demonstrate a significant lack of S100 immunoreactivity in metastatic UM, with 84.6 % of cases showing negativity, in contrast to the diffuse positivity seen in both primary UM and metastatic CM. This finding suggests that the absence of S100 could serve as a useful marker to differentiate metastatic UM from CM, especially in cases where the primary tumor is unknown. Furthermore, the study highlights the potential diagnostic pitfall of relying solely on S100 expression on small biopsies. The absence of S100 in metastatic UM may reflect a shift in antigenic expression, possibly due to tumor dedifferentiation or clonal selection of S100-negative cells with a higher metastatic potential. Our findings emphasize the importance of employing a comprehensive immunohistochemical panel, including markers such as HMB45, SOX10, and Melan-A, in the accurate diagnosis of metastatic melanomas.

1. Introduction

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults and accounts for approximately 3–5 % of all melanoma cases. It primarily arises in the uveal tract of the eye, with most cases involving the choroid (85–90 %), followed by the ciliary body (5–8 %) and the iris (3–5 %) [1-3]. Despite a relatively low incidence, UM has a high mortality rate due to metastasis, with up to 50 % of patients succumbing to the disease within 10 years of diagnosis [4]. Metastases, primarily affecting the liver, followed by lungs, skin, soft tissue, bone, and lymph nodes, develop through hematogenous spread rather than lymphatic dissemination, and frequently occur after 10–15 years after the first diagnosis. Once metastasized, the median survival is 6 to 12 months, and the 1-year survival rate drops to around 15 % [5].

According to the 8th edition of TNM staging, prognosis is influenced by the following factors: tumor location (iris melanomas have a lower mortality rate than posterior UMs); age and sex (younger patients and females tend to have better outcomes); histopathological features (infiltration of the ciliary body, extraocular extension, and thickness and basal diameter) [4-6]. In addition, mitotic activity (number of mitoses/mm^2) and Ki-67 proliferation score are also useful for assessing tumor aggressiveness [7-9].

The treatment options for primary UM include both globe-preserving therapies (radiation, laser, surgery) and enucleation, especially for large or recurrent tumors [9]. Metastasis management focuses on hepatic monitoring, given the liver's predilection as the primary metastatic site. Unfortunately, despite advancements in primary tumor treatments, overall survival rates have not significantly improved, with metastatic disease remaining difficult to treat [10-14]. The only therapeutic approach for metastatic UM is tebentafusp, approved by the FDA in 2022

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[15]. Immunotherapy, which is effective in cutaneous melanoma (CM), has not yielded favorable results in UM, likely due to differences in the tumors' biological and immunogenic properties [16,17].

UM differs significantly from CM in both genetic alterations and response to treatment. [18]. While UV exposure is a well-established risk factor for CM, its role in UM is unclear, with conflicting studies. Some suggest a weak association between UV exposure and UM, while others propose a protective effect for individuals with increased outdoor activity [19].

Histologically, the Callender Classification, originally describing six subtypes based on cellular morphology (spindle A, spindle B, fascicular, mixed, epithelioid, necrotic), has been simplified by the American Joint Committee on Cancer (AJCC) into three main subtypes: spindle, epithelioid, and mixed. Spindle cell UMs (exhibiting spindle cell morphology in 90 % of tumor) tend to have a better prognosis, while epithelioid cell UMs (exhibiting epithelioid cell morphology in 90 % of tumor) are associated with worse outcomes. Other rare morphological several variants of choroidal and ciliary body include diffuse UM (< 5 mm in thickness and occupying at least one quarter of the uveal tract); retino-invasive UM; ciliary body ring melanoma; clear cell melanoma; and cavitary UM [16]. Tumor-infiltrating lymphocytes (TILs) and specific vascular patterns also correlate with prognosis [20,21]. Higher TIL levels have been linked to worse outcomes in UM, despite their positive prognostic value in other cancers.

S100 is a family of calcium-binding proteins that are primarily found in nerve cells and glial cells (cytoplasmic and nuclear staining required to call positive). However, some S100 proteins have been found to be elevated in the blood of patients with certain types of cancer and may serve as serum tumor markers [22]. S100 measurements are now universally recommended in national and international guidelines on CM and belong to commonly available and routinely performed laboratory tests in the follow-up of melanoma patients [22].

In pathology diagnostic routine practice, the immunohistochemical expressions of S100 and SOX10 have been traditionally considered the most sensitive markers of melanocytic lineage/differentiation when dealing with a metastasis from unknown primary cancer. However, the majority of studies about S100 immunoreactivity in melanocytic neoplasms have always had CM as their main focus, while less is known about S100 expression in UM and metastases from UM. Accordingly, the aim of the present research was to evaluate the immunohistochemical expression of S100 in a single-institution series of metastases from UM and to compare it with its expression in metastases from CM and primary UMs.

2. Materials and methods

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the local Ethics Committee, Comitato Etico Catania 1, University of Catania (ID: 003186-24); 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.

The present retrospective study includes 41 patients, specifically 13 cases of metastatic UM, 10 cases of matched primary UM, and 18 cases of metastatic CM. In 3 out of 13 cases of metastatic UM, it was not possible to retrieve the matched primary tumor. No information about the primary CM cases were available. All these cases were retrieved from the pathology files of the archive of Department “G.F. Ingrassia”, University of Catania, Italy, from 2018 to 2024. Focusing on various clinical and pathological characteristics of the patients, the variables considered included: gender, age, tumor localization, histological type, and the expression of immunohistochemical markers of melanocytic lineage (Melan A, HMB45, SOX10, S100). We considered the immunohistochemical expression of Melan-A and HMB45 as positive when cytoplasmic staining was found, while SOX10 and S100 were assessed as positive if nuclear and both nuclear and cytoplasmic staining were, at least weakly and focally, seen, respectively.

Immunohistochemical analyses were conducted on formalin-fixed, paraffin-embedded tissue sections, employing heat-induced antigen retrieval, as previously reported [21]. We used a rabbit polyclonal antibody anti-S100 (ready to use; Dako, Glostrup, Denmark) developed against the bovine S100 protein fraction and reactive to both S100a and S100β, a rabbit monoclonal antibody anti-SOX10 (clone SP267; working dilution 1:100; Abcam, Cambridge, United Kingdom), a mouse monoclonal antibody anti-Melan-A (clone A103; working dilution 1:100; Thermofisher, Waltham, Massachusetts, United States), and a mouse monoclonal antibody anti-Human Melanosome (clone HMB45; working dilution 1:50; Dako, Glostrup, Denmark). A positive immunoreactivity was defined as showing at least weak and focal positivity (>5 % of neoplastic cells). All cases with negative or ambiguous staining were re-evaluated by two pathologists. Both positive and negative controls were included in the process.

3. Results

Regarding patients with metastatic UM, the average age is 65 years. The gender distribution shows a male predominance (69 % males vs 31 % females). A prominent feature of the data is the predominance of hepatic localization of the UM, observed in 92.3 % of the cases (12 cases). Histologically, most of these cases are classified as “epithelioid cells” or a combination of spindle and epithelioid cells. No cases exhibited a spindle cell morphology. In all cases of metastatic UM, the immunohistochemical expression of HMB45 and SOX10 showed diffuse positivity, while Melan-A was negative in only two cases. The analysis of immunohistochemical marker expression highlights a high rate of lack of S100 expression, with 84.6 % of the cases not expressing this marker (11 cases) (Fig. 1A-D).

About cases of metastatic CM, we observed the same average patient age (65 years) and a similar gender distribution (67 % male and 33 % female). The most common sites were the lymph nodes (8 cases), and the central nervous system (6 cases). Histologically, as in metastases from UM, the most represented histological subtype was epithelioid cell type (14 cases), while all other cases showed a combined spindle and epithelioid cell morphology. However, different immunohistochemical findings were seen. Melan-A and HMB45 were positive in all cases except for 4 (14 cases). SOX10 was positive in all cases. S100, on the other hand, showed diffuse positivity in all cases except one (17 cases) (Fig. 2 A, B). In detail, Table 1 summarizes the main demographic and immunohistochemical data of our cases of metastatic UM compared to those of metastatic CM.

The 10 cases of primary UM showed similar distribution, average age of onset, most frequent histological subtype, and expression of Melan-A, HMB45, and SOX10, comparable to the previously mentioned cases. However, the most significant finding concerns the expression of S100, which was positive in all cases, in contrast to the metastases from UM (Fig. 3A). We also noted that in 2 out of 10 cases, S100 exhibited a peculiar heterogeneous pattern of staining which consisted of areas of normal strong expression alternating with areas of total lack of expression (Fig. 3B, insert).

Table 2 compares in more detail the immunohistochemical results of the 10 cases of primary UM and their corresponding metastases.

4. Discussion

We observed a frequent lack of S100 immunoreactivity in UM metastases, a finding that stands in contrast to the widespread positivity seen in both primary UM cases and patients with metastatic CM. This differential expression of S100 could have important implications, not only because it represents an important diagnostic pitfall but also for potential differential treatment strategies tailored to these distinct melanoma types. Fig. 3A summarizes the main immunohistochemical findings of the present study across different melanoma cohorts.

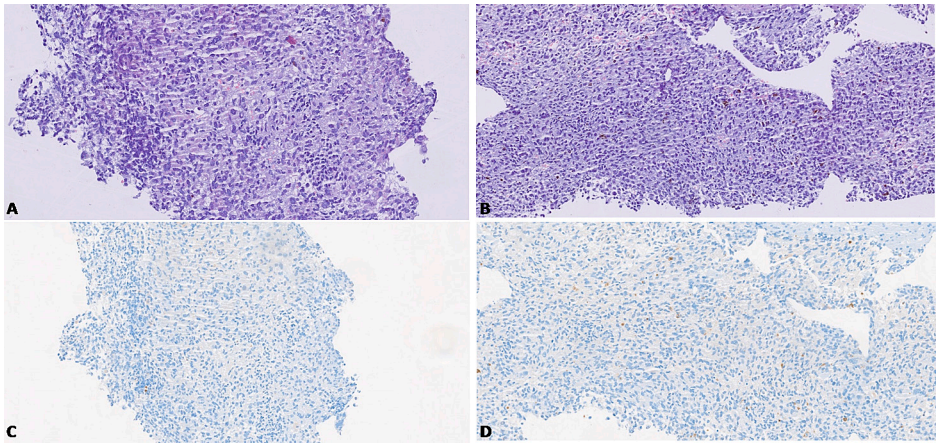

Fig. 1. Liver metastases from UM. (A,B) Two cases of liver metastases from UM from our series (hematoxylin and eosin; original magnifications 150×); (C,D) The lack of S100 expression is seen in both tumors (immunoperoxidase; original magnifications 150×).

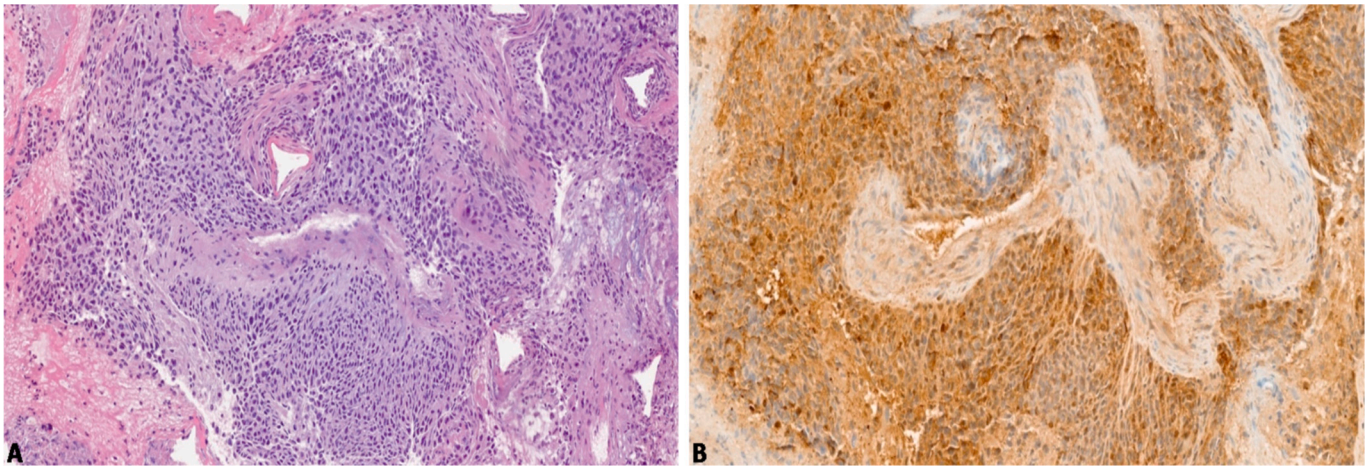

Fig. 2. Metastases from CM. (A,B) A metastatic CM showing diffuse S100 immunoreactivity (B) is seen (A, hematoxylin and eosin; B, immunoperoxidase; original magnifications 150×).

Table 1
Demographic data and staining results of UM vs CM.

	Metastatic UM	Metastatic CM
Number of cases	13	18
Gender distribution	31 % Female	33 % Female
	69 % Male	67 % Male
Median age	65	65
Histopathologic features	77 % epithelioid	78 % epithelioid
	23 % mixed	22 % mixed
HMB45 expression	13 Positive	14 Positive
	0 Negative	4 Negative
SOX10 expression	9 Positive	13 Positive
	4 Negative	5 Negative
MelanA expression	11 Positive	14 Positive
	2 Negative	4 Negative
S100 expression	2 Positive	17 Positive
	11 Negative	1 Negative

S100 protein has traditionally been considered a reliable marker in the identification of metastases from melanocytic tumors, including both cutaneous and UMs [22-24]. However, the reported absence of S100 expression in metastatic UM raises important questions about the molecular and cellular mechanisms underlying this phenomenon. One possibility is that S100α and S100β proteins, which are commonly detected by immunohistochemistry in melanoma, may either be absent in UM metastases or expressed in a form that is not recognized by the reagents used in these assays. This could suggest that ocular melanocytes, from which UM originates, produce molecular variants of S100 proteins, lacking the epitopes typically identified in CMs [22-24].

Understanding these molecular differences could prove critical in clarifying the relationship between cutaneous and UMs, which, while both derived from melanocytes, exhibit widely different biological and molecular characteristics. Historically, antigens identified in CMs have also been found in uveal melanomas, suggesting some shared antigenic properties. Nevertheless, the clinico-biological profiles of these two melanoma types diverge significantly, and the different patterns of S100 expression observed in our study could offer further insight into this divergence [22-24].

In diagnostic pathology, on one hand, the lack of S100 immunoreactivity in metastatic UM may represent a potential diagnostic pitfall, especially on small biopsies, while, on the other hand, it could serve as a useful marker to distinguish these tumors from metastases originating from CM. In this regard, we would like to emphasize that, if pathologists deal with a case of metastatic melanoma that is S100-negative but positive for other melanocytic markers such as Melan-A, HMB45, and SOX10, a potential origin from the uveal tract may be suggested in the pathology report. This could be particularly relevant in cases where the primary tumor is unknown or in instances in which the tumor has undergone dedifferentiation and thus exhibits altered antigenicity.

Our study, which focused on the analysis of S100 protein expression

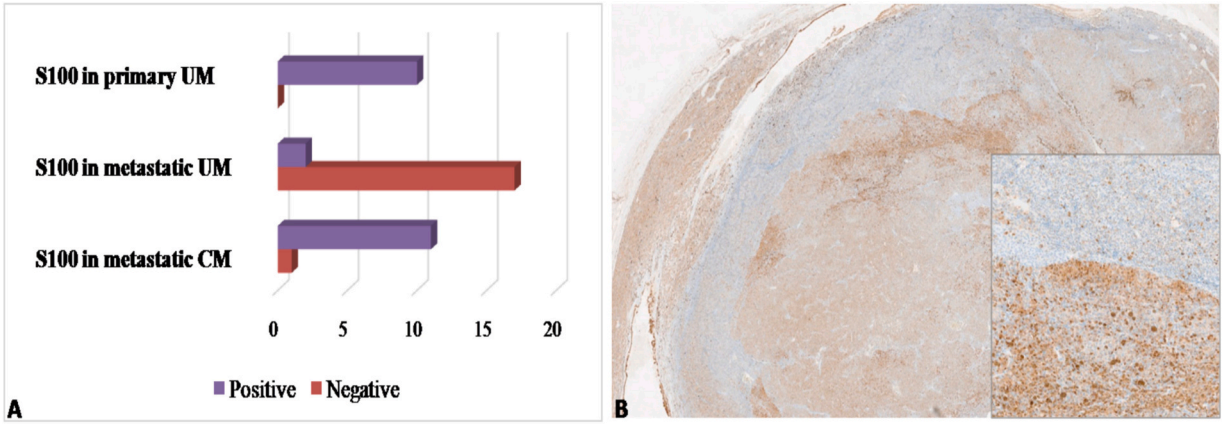

Fig. 3. S100 expression. (A) Distribution of S100 immunoreactivity in metastatic UM, primary UM and metastatic CM; (B) Primary UM with areas of diffuse S100 expression, alternating with areas lacking S100 immunoreactivity (insert) (immunoperoxidase; original magnifications 25× and 200×, insert).

Table 2
Comparison of the immunohistochemical expression of HMB45, MelanA, SOX10, and S100 in primary uveal melanomas and their corresponding metastases. +: positive expression; −: lack of expression.

	MelanA		HMB45		SOX10		S100	
	Primary	Metastatic	Primary	Metastatic	Primary	Metastatic	Primary	Metastatic
Case 1	+	+	+	+	+	+	+	−
Case 2	+	+	+	+	−	−	+	−
Case 3	+	+	+	+	+	+	+	−
Case 4	+	+	+	+	+	+	+	+
Case 5	+	−	+	+	+	+	+ (Heterogeneous)	−
Case 6	+	−	+	+	−	−	+	−
Case 7	+	+	+	+	+	+	+	−
Case 8	+	+	+	+	+	+	+	+
Case 9	+	+	+	+	+	+	+	−
Case 10	+	+	+	+	−	−	+ (Heterogeneous)	−

across different melanoma cohorts, demonstrated a remarkable pattern: 84 % of UM metastases were S100-negative. This was in strong contrast to the findings in primary UM cases, in which S100 expression was much more common. This shift in antigenic expression could reflect several underlying biological processes. One possibility is that tumor cells undergo dedifferentiation as the disease progresses, losing their original phenotypic characteristics, including S100 expression. Alternatively, the loss of S100 expression could result from clonal selection, where a subpopulation of tumor cells with a growth advantage emerges, leading to a more aggressive phenotype that is less reliant on the typical melanocytic markers.

This phenotypic shift may highlight fundamental intrinsic differences between uveal and cutaneous melanocytes, which, while both originating from neural crest cells, are influenced by distinct environmental and molecular cues in their respective tissues. These differences could be further compounded by the distinct immune microenvironments in the eye versus the skin, possibly contributing to the divergent S100 expression patterns.

Although S100 expression is generally strong and diffuse in primary UM, our findings suggest that there may be specific areas within the tumor in which S100 staining is absent (Fig. 3B). In this regard, we speculate on the intriguing hypothesis that metastatic spread may originate from the selection of these S100-negative regions within the primary tumor. If this is true, the absence of S100 in metastases may not merely be a result of dedifferentiation during metastatic progression but could reflect a pre-existing heterogeneity within the primary tumor. In other words, certain clones within the primary tumor that lack S100 expression may have a higher propensity to metastasize, suggesting a link between S100 negativity and metastatic potential.

In diagnostic practice, the utility of S100 as a diagnostic marker is well established. As noted by some colleagues [25], when pathologists deal with a poorly differentiated metastatic tumor, S100 is often included in the initial immunohistochemical panel, representing the most sensitive marker of melanocytic lineage, along with SOX10. However, based on our findings, the absence of S100 in metastatic melanoma (positive for at least one additional melanocytic marker) could carry further diagnostic significance, specifically pointing toward a potential uveal origin. In this regard we would like to emphasize the importance of using multiple melanocytic markers, even in double staining, including S100, SOX10, Melan-A, HMB45, and PRAME [11,26-29].

In addition, Salzmann et al. demonstrated that serum levels of S100 protein increase in patients with metastases that strongly express S100, while they remain stable in those without expression. However, S100 is not a sensitive biomarker for the early diagnosis of metastases, as its value depends on expression in metastatic lesions, which can be predicted through immunohistochemistry. Consequently, S100 may be useful for monitoring disease progression but is not reliable for the early diagnosis of advanced UM [30]. These authors also performed immunohistochemical analyses for S100 on a large series of UM tissue sample with conflicting results with those we herein obtained, with about 80 % of metastatic UM cases showing, at least focal and weak, S100 expression [30]. In our opinion this conflicting results might be explained by by the different S100 clones and the different immunohistochemical detection systems used. Furthermore, some colleagues suggest that circulating tumor cells (CTCs) in localized uveal melanoma can be used to identify prognostically significant structural chromosomal abnormalities (SCNAs), while ctDNA serves as a useful tool for detecting early signs of metastatic progression. This study highlights the potential of CTC and ctDNA analysis as a liquid biopsy to support treatment

decision-making in patients with uveal melanoma [31].

In conclusion, the lack of S100 expression in cases of metastatic UM should not be dismissed as merely a technical artifact or an anomaly but rather may serve as an important diagnostic clue. This S100-negative phenotype likely reflects specific cellular changes that occur during tumor progression in uveal melanoma. Understanding this point could aid in distinguishing UM from CM, particularly in metastatic settings where the primary tumor site is unknown. Moreover, the expression of other melanocytic markers such as Melan-A, HMB45, and SOX10 in S100-negative tumors further supports the utility of a broader immunohistochemical panel to confirm both melanocytic lineage and uveal origin.

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CRediT authorship contribution statement

Serena Salzano: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Giada Maria Vecchio:** Conceptualization. **Maria Failla:** Conceptualization. **Andrea Russo:** Methodology. **Teresio Avitabile:** Methodology. **Antonio Longo:** Methodology. **Rosario Caltabiano:** Writing – review & editing, Validation. **Giuseppe Broggi:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Compliance with ethical standards

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the local Ethics Committee, Comitato Etico Catania 1, University of Catania (ID: 003186–24). 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.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve the language and the readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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.

Data availability

All data generated in the present research are available from the corresponding author upon reasonable request.

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