

Melanoma Associated Leukoderma: Case Series and Literature Review

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Received September 02, 2022; Revised October 04, 2022; Accepted October 13, 2022

Abstract Vitiligo is an acquired achromia linked to an autoimmune destruction of melanocytes. One of its mysterious aspects is its occurrence with melanoma known as melanoma-associated leukoderma (MAL). The Objective of the study is to shed the light on the clinical aspects of MAL for a better understanding while providing a comprehensive review of the literature. We retrospectively analysed the clinical characteristics of 12 patients having MAL, from 2016-2021. We compared our findings to those reported in the literature. Our series illustrates different situations where vitiligo is linked to melanoma. None of our patients had a positive family history of vitiligo. The median age was 68 years with extremes of 90 and 36 years, 10 patients had their MAL located on photo-exposed areas. Clinically MAL presented as diffuse, macular achromic patches located primarily at sites distant from the primary melanoma and notably on the trunk, legs and face with a late age of onset. No histological particularities as opposed to vitiligo were found. Given the clinical similarities of these achromias with conventional vitiligo, a more thorough clinical examination for melanoma in patients with vitiligo seems to be crucial. Special attention is needed for older patients presenting with late onset, very progressive vitiligo-like lesions refractory to standard treatment.

Keywords: leukoderma, melanoma, vitiligo, hypopigmentation

Cite This Article: Hali Fouzia, Kerouach Amal, Belanouane Sarah, Chiheb Soumiya, El Hadigui Sofia, and Diouri Mounia, "Melanoma Associated Leukoderma: Case Series and Literature Review." *American Journal of Clinical Medicine Research*, vol. 10, no. 2 (2022): 36-41. doi: 10.12691/ajcmr-10-2-2.

1. Introduction

The presence of melanoma and vitiligo simultaneously in the same patient is considered a medical paradox, giving the fact that the first is characterized by a massive irregular proliferation of atypical melanocytes within the epidermis, while the latter is the result of progressive loss of functional epidermal melanocytes. This article provides an approach of the clinical features of Melanoma associated vitiligo (MAL) for a better understanding of this entity while providing a comprehensive review of the literature.

2. Material and Methods

In this case series, we retrospectively analysed the clinical presentation, type of depigmentation, and disease course of patients with MAL who were diagnosed at the Dermatology Department of IBN ROCHD University Hospital in Casablanca, from 2016-2021. As no approved definition of MAL currently exist, we arbitrarily defined MAL as any achromic lesions present before, concomitantly or after the diagnosis of melanoma. When

other causes of leukoderma were suspected, biopsy was performed to discard differential diagnosis. Patients characteristics, including demographic, clinical, pathological, and follow-up, were anonymously extracted from the patients medical records.

This study was carried out in accordance with the principles set out in the Declaration of Helsinki and local ethical guidelines (Ethics Committee for Biomedical Research, Faculty of Medicine and Pharmacy, Casablanca, Morocco).

As no procedures other than standard of care and anonymized and observational data analysis were performed during the study, no additional ethics committee approval was necessary.

3. Results

In the period of the study, 130 patients with melanoma were hospitalized and Twelve patients with MAL were identified which gives us a roughly prevalence of 9,2 %. All of our patients were of phototype IV; the median age was 68 years. The bilateral and symmetrical pattern was found in Ten patients and the distribution was mostly generalized to the face, trunk, back and legs, but in one patient with acral melanoma on his right foot, the MAL

was mostly dispatched on the same side of the malignant tumor (Figure 1d). All of our patients had their MAL located at distance of their primary melanoma, although in one patient (Figure 1a), MAL presented as a white halo surrounding the melanocytic lesion. Ten patients had their MAL located on photo-exposed areas, and Two on the back. None of them had a positive family history of vitiligo. The clinical presentation consisted mostly of well-demarcated achromic patches. Lesions were generally refractory to topical steroids and UV phototherapy. Out of the twelve patients, five had MAL prior to melanoma, five after the onset of melanoma, one following interferon treatment, and in one patient both diseases appeared concomitantly. Nine patients out of twelve had a stage IV melanoma, four of which had MAL after the malignant diagnosis. Five patients (Figure 2a, Figure 2b, Figure 2c, Figure 3b, Figure 3d) with MAL diagnosed prior to melanoma were

staged IB, IA, and IV for the last three patients respectively. Extreme latency periods going from 10 years prior to 10 years after the melanoma diagnosis were noted. In the setting where MAL preceded melanoma (5 patients), none of our patients consultation was motivated by the appearance of the vitiligo-like lesions except for one (Figure 2a), she was diagnosed by her dermatologist while consulting for vitiligo. Two patients (Figure 2c, Figure 3b) consulted after their melanoma got ulcerated and enlarged, and the last patient (Figure 2b) reported that she became esthetically bothered and worried about the pigmented lesion on her face, which proved later to be lentigo maligna melanoma (LMM). Histological analysis was performed in eight patients showing a total absence of functioning melanocytes in the lesions, in keeping with Vitiligo. Clinical characteristics of these patients are summarized in Table 1.

Table 1. Clinical characteristics of patients with MAL

	Age /sex	Type/Breslow/ Clark/ location of primary melanoma	Onset/Diagnosis	Time lapse between diagnosis and MAL	Location MAL/type	HISTORY/ malignancy/ Autoimmune disease	Histological finding MAL	-Metastases -Stage (8th AJCC)	Follow up
1a	76/M	SSM/2.5mm/ III/perianal	4 months	2 months after	Perianal (Sutton's nevus) Face, hands Scalp, legs/ Bilateral Symmetrical	Diabetes mellitus (adult onset)	Consistent with vitiligo	-None -Stage IIB	Living (5Years follow-up)
1b	57/M	SSM/13mm/V/ sole	4 months	2 months following interferon treatment	Face , forearms /Bilateral Symmetrical	Diabetes mellitus (adult onset)	Disappearance of skin melanocytes	-Peritoneal carcinomatosis/ nodal metastasis -Stage IV	Death
1c	70/M	NM / 12mm/V/ the back	2 months	Concomitant	Lumbo-sacral region Legs and forearms/ Symmetrical	no	Consistent with vitiligo	-Abdominal, Prostate metastases -Stage IV	Death two years after onset
1d	69/M	ALM/ 2mm/III/ sole	20 years	12 years after	Started on the face and hands then DIFFUSE Bilateral asymmetrical	Papillary urothelial Carcinoma (Low grade)	Disappearance of skin melanocytes	-Nodal, Abdominal, pelvic metastases -Stage IV	Death
2a	64/F	ALM/1.5mm/IV/s ole	4 months	10 years prior	Peri-oral/ Bilateral Symmetrical	no	Consistent with vitiligo	-None -Stage IB	Living (2 years follow-up)
2b	70/F	LMM/0,6mm/face	2 years	5 years prior	The back/ Bilateral Symmetrical	no	-	-None -Stage IA	Living (3 years follow-up)
2c	36/F	Nodular/2.8mm/V /under left breast	3 years	Undetermined number of Years prior	Diffuse Bilateral Symmetrical	no	Vitiligo	-Lung, liver metastases -Stage IV	Lost of follow up
2d	67/F	Nodular/2mm/V /under right breast	2 years	2 years after	Acro-facial /Bilateral Symmetrical	no	-	-C7 and axillae metastases -Stage IV	Living (8 months)
3a	81/M	Nodular/5mm/IV/ sole	20 years	10 years after	Scalp /Bilateral Symmetrical	no	-	-Liver, Bone metastases -Stage IV	Living (9 months)
3b	90/F	ALM/18mm/IV /s ole	One year	4 months prior	Bilateral And symmetrical /Back	Breast cancer	-	-Lung metastases -Stage IV	Living (6 months)
3c	71/M	ALM/12mm /IV/s ole	2 years	2 months after	Bilateral Symmetrical Face/ forearms	no	Disappearance of skin melanocytes	-Nodal Brain metastases -Stage IV	
3d	72/F	ALM/8mm /IV/so le	4 years	4 months prior	Bilateral Symmetrical/Face	no	Disappearance of skin melanocytes	-Lung, Liver metastases -Stage IV	

Key: SSM: Superficial spreading melanoma; ALM: Acral lentiginous melanoma; LMM: lentigo maligna melanoma; NM: nodular melanoma.



Figure (1a)

Figure (1b)

Figure (1c)

Figure (1d)

Figure 1. anal, dorsal and plantar melanoma associated leukoderma



Figure (2a)

Figure (2b)

Figure (2c)

Figure (2d)

Figure 2. Melanoma of dubreuil, plantar melanoma and sub mammary melanoma associated leukoderma



Figure (3a)

Figure (3b)

Figure (3c)

Figure (3d)

Figure 3. Plantar and intertortil melanoma associated leukoderma

4. Discussion

MAL is reported in the literature under different appellations such as Melanoma associated leukoderma (MAL), Melanoma associated vitiligo (MAV); Melanoma associated hypopigmentation (MAH) or Melanoma-associated depigmentation (MAD).

The incidence of MAL seems to be very low, Koh et al [1] reported only eight cases in 14 years, and Schrollreuter et al. examined 623 patients with melanoma to only yield the MAL in 23 cases (3,7%). [2]

Several studies showed that spontaneous MAL in individuals with melanoma is significantly more common than in the general population [2,3,4]. A prospective study of 2954 patients with melanoma of all stages found the prevalence of vitiligo was 2.8%, compared with 0.4–2% in the greater population [5]. Paradoxically, a series of 1052 vitiligo patients revealed only 3 cases of melanoma (0.3%), which is a lower incidence of melanoma than in the general population [6]. Immunotherapy probably increases the incidence of vitiligo associated with melanoma [4,7].

MAL can either spontaneously precede, follow the onset of melanoma, or more commonly occur following treatment [4,6,7,8,9]. Although in 79.5% of cases MAL is diagnosed after the onset of melanoma [5], leukoderma can be a premonitory symptom occurring months to years, before the diagnosis of the malignancy is made.

Different forms of MAL were reported in the literature: (1) A white halo surrounding the melanocytic lesion (Sutton's nevus), (2) achromic patches located in the melanoma scar, (3) complete or partial regression of the melanoma [10]. Rarely, (4) MAL manifest as white patches distant from the primary lesion, arising either spontaneously or following immunologic-based treatments.

Our series illustrates different situations where vitiligo is linked to melanoma. In Table 2, we represent a comparative analysis of some case series of MAL reported in the literature. Many of these series, considered MAL as a side effect linked to treatment good response, however in our patients, all but one (Figure 1b) had their MAL appear independently of any treatment, which may suggest that MAL, besides being a therapeutic goal, is also an independent indicator of the autoimmunity effectiveness against melanoma.

Several studies sought to clarify if vitiligo and MAL are distinct clinical entities [4,8,11,12]. The clinical, histological, and immunohistological differences between MAL and classic vitiligo are not well established. Vitiligo is triggered by both genetic and environmental factors, whereas MAL is triggered by the presence of melanoma. With the heavy consequence of misdiagnosing patients as having vitiligo and later developing melanoma metastases.

Table 2. Comparative analysis of some case series of MAL reported in the literature.

Autor	Type etude	year	Number of patients	Treatment	Time lapse between MAL and melanoma onset	Incidence of MAL	Conclusion
Hua et al. [9]	Observational Prospective (over 1 year and 9 months)	from January 1, 2012, through September 24, 2013,	67	Pembrolizumab	The time to onset of vitiligo ranged from 52 to 453 (median, 126) days from the start of treatment. (pembrolizumab)	25%	Vitiligo, a clinically visible immune-related adverse event could be associated with clinical benefit in the context of pembrolizumab treatment.
Boasberg et al. [31]	Retrospective (duration depends on the treatment period)	2006	49	Various (chemotherapy, IL-2, INF-a and GMCSF)	Vitiligo was developed after treatment and the median onset was 35 days	43%	Improved median survival for people who developed vitiligo compared to the who did not.
Hwang et al. [33]	Retrospective (over 2 years and 8 months)	2016	82	Pembrolizumab Nivolumab	Vitiligo was considered as a cutaneous immune adverse event and a response indicator after treatment initiation and was seen in patients within 10.3 months of therapy.	15%	Lichenoid reactions, eczema, and vitiligo were the 3 most prevalent irAE's in melanoma patients treated with immunotherapy
Babai et al. [32]	Retrospective (between the beginning of the commercialization of ICI in France and 1 January 2019)	2020	67	pembrolizumab, nivolumab and ipilimumab	the median times to onset of vitiligo after the start of pembrolizumab, nivolumab and ipilimumab therapies were 5.4, 5.0, and 3.8 months, respectively.	Among the 95 vitiligo cases, 74 (78%) occurred with pembrolizumab, 13 (14%) with nivolumab, 6 with ipilimumab, and 2 with ipilimumab/nivolumab	Suggestion that the resolution of pembrolizumab- or nivolumab-induced vitiligo could be a marker of disease progression.
Lommerts et al. [13]	Blinded comparison study between MAL and vitiligo (over 5 years)	2015	11 with MAL 33 with vitiligo	n/a	A median of 2.3 after diagnosis of melanoma	25%	Clinical discrimination between MAL and vitiligo is difficult, due to the lack of discriminative features.
Iglesias et al. [34]	Prospective observational	2018	2	Talimogene Laherparepvec (T-VEC)	MAL appeared two months after the last drug administration (14 every 3 weeks)	n/a	Complete response after T-VEC treatment for both patients.
Hartmann et al. [8]	Prospective (over 5 years)	2008	12	n/a	Mean onset was 4.8 years after the primary diagnosis of the melanoma. Three melanoma patients reported hypopigmentation more than 15 years before diagnosis of melanoma		MAL was less progressive compared to vitiligo; Histological and immunohistological differences were not found.
Lindlof et al. [6]	Retrospective over 21 years	1992	3		In two cases the vitiligo developed after diagnosis of melanoma and in one case 32 years before.	0,3%	Only 3 patients out 1052 over a 21 years period The association was not significant
Our series	Retrospective over 5 years	2016 to 2021	12	Various (chemotherapy, surgery, INF-a, Immunotherapy)	Out of the Twelve patients, five had MAL prior to melanoma, five after the onset of melanoma, one following interferon treatment, and in one patient both diseases appeared concomitantly.		Clinically MAL presented as diffuse, macular achromic patches located primarily at sites distant from the primary melanoma and was frequently on the trunk, legs and face with a late age of onset. No histological particularities as opposed to vitiligo were found.

In MAL, lack of family history of vitiligo or atopy, advanced age of onset, predominance in photo-exposed areas and generalized distribution are found to be discriminative features [8,11,12]. Notwithstanding, histological and immunohistological differences have not been found. Accordingly, none of our patients had a positive family history of vitiligo. The median age of our patients was 68 years with extremes of 90 and 36 years and the most of our patients (10/12) had their MAL located on photo-exposed areas. This correlates with other case series in which a positive family history of vitiligo was absent in all patients with MAL [8,12]. In contrast, Lommerts et al reported that 9.1% of the patients with MAL had a positive family history of vitiligo [13]; patients with history of autoimmune disease encounter the risk of having their MAL diagnosed as vitiligo vulgaris, without prompting the clinician to inspect further for melanoma.

Lommerts et al. also reported that experts in the field blindly examined photographs of 33 patients with vitiligo and 11 patients with MAL; as a result, 80% of MAL were misdiagnosed as vitiligo based on clinical presentation. Therefore, the authors proposed the term melanoma associated vitiligo (MAV) as no discriminative features were found [13].

Similarly, Hartmann et al. performed clinical, histological, and laboratory tests to evaluate the similarities and differences between MAL and classic vitiligo. MAL lesions, just like vitiligo, were most often distributed in a bilateral symmetrical pattern but less progressive. He reported that MAL was more often associated with other acquired leukodermas. Again, histological and immunohistological discriminative features were not found [8]. The symmetrical bilateral pattern was noted in all our patients, and the results of the biopsies we performed on the achromic patches were in keeping with vitiligo.

The depigmentation is a result of a strong autoimmune anti-melanoma defense that also targets healthy melanocytes due to shared expression of differentiation antigens. In fact, the melanoma-specific cytotoxic T lymphocytes (CTLs) are able to recognize melanocytes antigens (Gp100, MART-1, Tyrosinase and Tyrosinase relating protein-2) on both normal and atypical melanocytes. Their presence in the blood and skin surrounding the tumor indicate that melanoma cells do not dodge the immune system [4,14,15]. The frequency of CTLs recognizing melanoma antigens appears to be higher in patients with metastatic disease than in those with primary tumors suggesting that a higher antigen index is associated with tumor progression [11,15,16]. Recently, there have been reports of a patient who developed unusual inflammatory vitiliginous skin lesions after an infusion of MART-1-specific CTLs [15]. Further, the report of Becker et al [17] demonstrated that the lymphocytes of the regression areas of melanomas were the very same as those of nearby hypopigmented areas. However, the presence of regression is paradoxically reported to carry a worse prognosis [18].

Rosenberg et al. reported that the majority of patients with metastatic melanoma treated with autologous tumor infiltrating lymphocytes developed leukoderma after melanoma regression, suggesting that a large infiltration of CTLs in the blood or skin surrounding the tumor is related to a better prognosis in these patients. [19]

Byrne et al. investigated the link between destruction of melanocytes in MAL and CTL reaction to melanoma. They uncovered that melanocyte antigens released by the process of MAL plays a major role in the maintenance of the long-term functional memory T cell response against melanoma [20]. This process might explain the complete or partial regression in some cases.

Recent studies found similar antibody patterns in patients with widespread vitiligo and with metastatic melanomas [21,22]. They showed that autoantibodies isolated from vitiligo patients targeted melanoma cells, suggesting that the same autoimmune mechanism is responsible for vitiligo and MAL. This suggestion needs further confirmation giving that in contrast Teulings et al. studied 7 patients with MAL and 27 patients with vitiligo and found that antibodies against MART-1 were only present in MAL and not vitiligo [23].

According to the Vitiligo Global Issues Consensus Conference, MAL cannot be classified as a subtype of vitiligo [8, 24]. We can deduct according to the literature reports above mentioned, that the only difference between MAL and vitiligo is the absence of melanoma in the latter.

The most interesting and last aspect of this association is its significance in terms of prognosis. Almost all studies demonstrated a higher incidence of metastatic disease in MAL patients than those with melanoma of comparable (Breslow) thickness, yet their overall survival rate was higher [7,25,26,27,28]. In our series, MAL enabled early diagnosis of melanoma in only one out of the 12 cases (Case 5). It has been suggested that preceding MAL could be an early warning sign of impending melanoma metastases.

MAL carries a better prognosis with an improved 5-year survival compared to melanoma patients of the same stage who do not have the associated depigmentation. [4,8,20]

A retrospective study indicated that melanoma patients with concomitant leukoderma had a higher survival rate [29], we only had one patient that developed both diseases simultaneously; he died two years after diagnosis of melanoma.

The authors propose topical corticosteroids with phototherapy to treat MAL, and patients should be encouraged to pursue anti-melanoma therapy despite the appearance of MAL as a side effect [30], these treatments both proved to be ineffective for our patients. Patients with MAL should probably be advised not to rush treatment for their MAL lesions given its potentially good prognostic value.

In this review, several aspects of the melanoma/vitiligo relationship are looked into, underlining the characteristics of the immune system responses shared by melanoma and vitiligo patients and the value of MAL as probably a biomarker for melanoma.

We are aware that the small sample size of our case series makes it difficult to determine the statistical validity of our suggestions, therefore further studies are necessary to better elucidate this intriguing association, as it will provide a clear understanding of immunologic regulation in vitiligo and melanoma, which might represent the corner stone to future therapeutic approaches to both diseases.

In conclusion, clinicians should be aware of the differential diagnosis of MAL when diagnosing vitiligo, which may enable an early diagnosis of melanoma by

thoroughly examining patients with leukoderma for other suspected pigmented lesions.

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