Melanoma-associated leukoderma and vitiligo cannot be differentiated based on blinded assessment by experts in the field

Janny E. Lommerts, MD,[a] Hansje-Eva Teulings, MD, PhD,[a] Khaled Ezzedine, MD, PhD,[b] Nanja van Geel, MD, PhD,[c] Anke Hartmann, MD, PhD,[d] Reinhart Speeckaert, MD, PhD,[c] Phyllis I. Spuls, MD, PhD,[a] Albert Wolkerstorfer, MD, PhD,[a] Rosalie M. Luiten, PhD,[a] and Marcel W. Bekkenk, MD, PhD[a]

Amsterdam, The Netherlands; Paris, France; Ghent, Belgium; and Erlangen, Germany

Background: Melanoma-associated leukoderma (MAL) is a depigmenting disorder that can occur spontaneously in patients with melanoma. The differences in clinical presentation between MAL and vitiligo are not well defined. This may lead to misdiagnosing MAL as vitiligo, resulting in delayed detection of melanoma.

Objective: The objective of this study was to assess whether experts in the field can distinguish between MAL and vitiligo, and to assess if discriminative features can be identified.

Methods: We designed an image comparison study in which 4 experts in the field blindly assessed photographs followed by medical history of 11 patients with MAL and 33 with vitiligo.

Results: The assessors misdiagnosed 72.7% of MAL cases and marked 80.0% of them as typical vitiligo. The median age at onset of the leukoderma was higher (55 years, $P = .001$) in MAL. No discriminative features were found.

Limitations: Sampling bias because of inclusion in tertiary referral center is a limitation.

Conclusion: The clinical presentation of leukoderma in patients with melanoma resembles that of vitiligo. We propose "melanoma-associated vitiligo" as the more appropriate term for leukoderma in patients with melanoma. Clinicians should be aware that depigmentation in vitiligo can also be caused by melanoma-associated vitiligo and a total body inspection should be performed. (J Am Acad Dermatol 2016;75:1198-204.)

Key words: clinical presentation; depigmentation; diagnostic accuracy; melanoma; melanoma-associated hypopigmentation; melanoma-associated leukoderma; melanoma-associated vitiligo; vitiligo.

Vitiligo is the most common depigmenting skin disorder affecting approximately 0.5% to 1% of the world's population.[1] Diagnosis of vitiligo is based on clinical presentation with symmetric distribution of well-demarcated depigmentations.[2] Probably the most alarming differential

Abbreviations used:

MAL:	melanoma-associated leukoderma
NIPD:	The Netherlands Institute for Pigment Disorders
NPV:	negative predictive value
PPV:	positive predictive value

From The Netherlands Institute for Pigment Disorders and Department of Dermatology, Academic Medical Center, University of Amsterdam[a]; Epidémiologie en Dermatologie et Evaluation des Thérapeutiques, Université Paris-Est, Service de Dermatologie, Hôpital Henri Mondor[b]; Department of Dermatology, Ghent University Hospital[c]; and Department of Dermatology, University of Erlangen.[d]

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Reprint requests: Janny E. Lommerts, MD, Department of Dermatology, Academic Medical Center, PO Box 22660, 1100 DD, Amsterdam, The Netherlands. E-mail: j.e.lommerts@amc.nl.

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diagnosis of vitiligo is melanoma-associated leukoderma (MAL). Depigmentation in MAL can occur spontaneously before or after the detection of melanoma.[3,4] A recent observational study showed that leukoderma occurs in 2.8% of all patients with melanoma and before the diagnosis of melanoma in 20.5% of all MAL cases.[5]

The differences and similarities in clinical presentation between MAL and vitiligo are not well defined and the literature is contradictory. A retrospective analysis found in the majority of patients with MAL a symmetric bilateral distribution in MAL similar to that in vitiligo.[4] However, other studies showed a more varied clinical spectrum between MAL and vitiligo with mostly hypopigmented macules with irregularly shaped borders and confetti-like appearance in MAL as opposed to the well-demarcated white macules in vitiligo.[2,6,7] The clinical presentation of MAL is sometimes described as atypical and not comparable with vitiligo.

CAPSULE SUMMARY

- Differences between the depigmenting skin disorders melanoma-associated leukoderma and vitiligo are not well defined.
- Experts in the field cannot clearly differentiate between vitiligo and melanoma-associated leukoderma based on clinical presentation.
- Clinicians should be aware of the differential diagnosis of melanoma-associated leukoderma when diagnosing vitiligo.

To date, in clinical practice it can be difficult to distinguish between MAL and vitiligo. Subsequently, these difficulties may lead to misdiagnosing the leukoderma in MAL as vitiligo resulting in late detection of melanoma. The aim of this study was to identify whether experts in the field can distinguish between MAL and vitiligo, and to assess if discriminative features can be identified.

METHODS

We conducted a blinded comparison study of clinical photographs at The Netherlands Institute for Pigment Disorders (NIPD) in Amsterdam. The local ethics committee stated that the Medical Research Involving Human Subjects Act was not applicable. Patients with MAL were retrospectively recruited from July 2010 until February 2015 and prospectively recruited from February 2015 until August 2015. MAL was defined as onset of leukoderma 1 year before the diagnosis of a primary melanoma, 3 years before the detection of melanoma metastases with an unknown primary tumor, onset of leukoderma after diagnosis of melanoma, or after immunotherapy. Patients with MAL were only included when all existing depigmentations were photographed. The medical records were used to extract patient characteristics.

Patients with vitiligo were prospectively and consecutively included until the ratio 1:3 of patients with MAL and vitiligo was reached. The inclusion criteria for vitiligo were as follows: (1) first presentation with vitiligo at the NIPD; (2) diagnosis of vitiligo; (3) Fitzpatrick skin type of I, II, III, or IV; and (4) age 18 years or older. Exclusion criteria were: not willing or able to give written informed consent or patients receiving ultraviolet B treatment in the past 6 months. Eligible patients with vitiligo were asked to fill in a questionnaire comprising questions regarding current age, skin type, gender, disease activity (vitiligo disease activity score), age at onset of leukoderma, family history of vitiligo, autoimmune comorbidity, and Koebnerization. Subsequently, photographs of all depigmentations were taken by our photography department. From all eligible participants written informed consent was obtained. Furthermore, a total body examination of all patients was performed.

Clinical assessment by experts in the field

All digital photographs and medical history of patients with both MAL and vitiligo were extracted and randomly presented in a digital form. The blinded assessment of patients was performed by 4 experts in the field (K. E., N. v. G., A. H., and R. S.). The ratio of patients with MAL and vitiligo was not known to any of the assessors. The questionnaire was divided into 2 parts: (1) assessment based on photographs; and (2) assessment based on photographs and medical history. In the first part of the questionnaire the assessors were asked to give their diagnosis (MAL or vitiligo), answer the question "I am certain of my diagnosis" on a Likert-scale, specify in case of vitiligo whether it is typical or atypical vitiligo, evaluate different clinical features, and state on which clinical signs the diagnosis was based. In the second part of the questionnaire, the assessors were asked whether the medical history (excluding potential history of melanoma) changed the diagnosis. If this was the case, they rated the certainty of their changed diagnosis and marked on which features the new diagnosis was based.

Data extraction and analyses

The data were extracted and statistical analyses were performed using software (SPSS, Version 22,