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Hypochromic vitiligo: delineation of a new entity

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Summary

Background Hypochromic vitiligo is a rare entity that has been reported only twice under the term 'vitiligo minor', with an absence of clear delineation.
Objectives To delineate hypochromic vitiligo through a case series of patients with typical bilateral hypopigmented lesions affecting the face and trunk.
Methods This is a retrospective multicentric evaluation study conducted in eight departments of dermatology in France, Belgium, Senegal and Saudi Arabia.
Results Twenty-four cases of hypochromic vitiligo were identified. Fourteen were men and 10 women. The mean age at diagnosis was 35·4 years (range 8–66). Strikingly, all patients were dark skinned, with skin types V and VI. The pattern of distribution was highly similar in most of the patients (18 of 24), with involvement of the face and neck area predominating on seborrhoeic areas associated with multiple isolated hypopigmented macules involving predominantly the scalp. The retrospective nature of this study is its main limitation.
Conclusions Hypochromic vitiligo is not yet part of a conventional classification. The disease seems to be limited to individuals with dark skin types. Hypopigmented seborrhoeic face and neck involvement associated with hypopigmented macules of the trunk and scalp is the hallmark of the disease.

What's already known about this topic?

- The classification of vitiligo has important implications.
- Few observations of vitiligo minor/hypochromic vitiligo, a rare entity affecting mainly individuals with dark skin types, have been reported.

What does this study add?

- We herein delineate a new entity that we called 'hypochromic vitiligo' through a case series of 24 patients with typical clinical presentation.

Vitiligo, the most common depigmenting disorder, is an acquired disease characterized by a progressive loss of melanocytes. Vitiligo occurs worldwide with an estimated prevalence of 0·5–1% in population-based studies. In almost half of the patients, vitiligo starts before the age of 20 years, and both sexes are equally affected.[1] In 2007, the Vitiligo European Task Force proposed consensus definitions that were further revised in 2012 by an international group of experts.[2,3] According to this classification, vitiligo can be categorized into two major forms: (i) nonsegmental vitiligo (NSV) (or vitiligo, including mixed vitiligo) and (ii) segmental vitiligo. Clinically, NSV, the most common form of the disease, is charac-

terized by symmetrical bilateral depigmented macules. Mixed vitiligo is the association of characteristic segmental involvement associated usually in a second step with the onset of bilateral vitiligo patches.[4] Of note, vitiligo macules can be transiently hypopigmented at their onset or when vitiligo is unstable and spreading.[5] Wood's lamp examination allows discrimination between hypopigmentation and completely depigmented lesions, which are highly suggestive of vitiligo. However, hypopigmentation should prompt consideration of differential diagnoses, mainly cutaneous T-cell lymphoma (CTCL) and various postinflammatory dermatoses.

Hypochromic vitiligo is a rare form of vitiligo, so far described only in dark-skinned individuals, characterized by the presence of hypopigmented lesions alone or associated with suggestive achromic macules, which arise without any preceding inflammation. Although this entity has been mentioned in recently published works,[3,6] no study on series of patients has yet attempted to define the condition adequately.

Here we present a case series of 24 patients with hypochromic vitiligo with the aim of better delineation of this yet undescribed entity.

Patients and methods

We conducted a multicentre retrospective study in eight departments of dermatology in France, Belgium, Saudi Arabia and Senegal. All patients were identified with a suspected diagnosis of hypochromic vitiligo, defined as acquired bilateral hypopigmented patches after the exclusion of other nonsegmental hypomelanoses, including CTCL and postinflammatory hypopigmentation. All patients were examined using Wood's lamp. Scotch tests with direct mycological examination were performed. When possible, biopsies were obtained from a hypopigmented macule and surrounding healthy skin for histological confirmation. Haematoxylin and eosin, haematoxylin–eosin–safran and melanin staining were performed in addition to an immunohistochemical study aiming to identify melanocyte repartition using HMB45 antibodies (Dako France, les Ulis, France). Clinical notes were retrospectively reviewed and the following specific variables were retrieved for each patient: age at consultation, age at disease onset, disease duration and distribution, presence or absence of concomitant depigmented areas, presence of leucotrichia, family history of vitiligo, personal and/or family history of autoimmune diseases, Koebner phenomenon, presence of mechanical triggering factors, and response to any treatment.

Results

The individual clinical and demographic data of the patients are presented in Table 1. Descriptive characteristics of the total population are presented in Table 2. Overall, 24 subjects fitting the case definition were identified. Fourteen were men and 10 women (female-to-male ratio 1 : 1·4). The mean age at diagnosis was 35·4 years (range 8–66). Strikingly, all patients were dark skinned, with skin types V and VI. In all patients, the differential diagnosis of hypopigmented dermatoses was excluded; these included postinflammatory hypopigmentation, mycosis fungoides, leprosy, seborrhoeic dermatitis, pityriasis versicolor, pityriasis lichenoides chronica, progressive macular hypomelanosis and atopic dermatitis. In addition, none of the patients had signs of inflammation, scaling or hypoesthesia, or a clear/pronounced skin infiltration. Potassium hydroxide wet-mount examinations were negative in all patients. Wood's lamp examination confirmed the hypopigmentation and the absence of fluorescence. Leucotrichia was absent in all patients. Eight patients (33%) had disease onset before the age of 20 years. The mean disease duration was 12·3 years (range 1–42). Of note, completely depigmented isolated macules were observed in only five patients (21%), who otherwise had typical hypopigmented face, neck and trunk involvement (Fig. 1). Twenty-one patients were treated with conventional vitiligo treatments, for example narrowband ultraviolet B, ultraviolet A, topical corticosteroids and tacrolimus. Response to treatment was overall very poor. Only three patients reported a partial response, and no patient had a complete response (Table 1). The pattern of distribution was highly similar in most of the patients (18 of 24), with involvement of the face and neck area predominating on seborrhoeic areas, associated with multiple isolated hypopigmented macules predominantly involving the scalp (Fig. 1a), the limbs and/or the trunk (Fig. 1b, c). A family history of vitiligo was present in five of the patients (patients 7, 8, 10, 16 and 19). The presence of typical Koebner phenomenon based on clinical examination was uncommon, and present in only four patients. Personal history of associated autoimmune disorders was present in five of the 24 patients (21%). Histopathology was performed in 18 patients. In all cases the patterns were similar, with an irregular decrease of melanin associated with a decrease in the number of melanocytes in hypopigmented areas, compared with the surrounding healthy skin (Figs 2, 3). No obvious signs of inflammation and no atypical lymphocytes located at the dermoepidermal interface were observed.

Discussion

The name hypochromic vitiligo refers to the mostly partial defect in pigmentation associated with rare completely depigmented macules. We have previously mentioned this entity in two reports, although its clinical spectrum was not then clearly delineated.[3,6] This first case series of hypochromic vitiligo allows us to define clearly the clinical spectrum of this potentially misleading entity. The first diagnosis that should be evoked when observing hypopigmented lesions is postinflammatory hypopigmentation. Seborrhoeic dermatitis should be discussed first because of the striking facial seborrhoeic localization observed in most of the patients with hypochromic vitiligo. However, several clinical signs argue against this diagnosis. The stability of lesions over time, the absence of signs of obvious inflammation, and no fluorescence on Wood's lamp examination are striking. In addition, most of

Table 1 Individual descriptions of 24 patients with segmental or nonsegmental hypochromic vitiligo

Patient, sex	Age (years)	Disease duration (years)	Type of distribution	Phototype	Site of lesions; total body surface area involved	Depigmentation on scars/ Koebner phenomenon	Presence of concomitant depigmented macules	Personal history of other autoimmune diseases	Familial history of vitiligo	Family history of other autoimmune diseases	Response to treatment
1, female	39	1	Nonsegmental	VI	Face and neck, limbs; 3%	No	Yes, one lesion	No	No	No	No
2, male	42	33	Nonsegmental	VI	Face and neck, scalp, limbs, trunk; 10%	No	Yes, sparse	No	No	No	No
3, female	30	4	Nonsegmental	VI	Face and neck	No	No	Yes, Graves disease	No	No	No
4, female	34	8	Nonsegmental	V	Face and neck, scalp, trunk, limbs; 12%	No	Yes, very few	Yes, Hashimoto thyroiditis	No	No	No
5, female	33	2	Nonsegmental	VI	Widespread; 47%	Yes	Yes, very few	Yes, urticaria	No	Yes, thyroid disease	Yes, partial
6, male	62	23	Nonsegmental	VI	Face and neck, scalp, limbs, trunk; 12%	No	No	No	No	No	Yes, partial
7, female	8	2	Nonsegmental	V	Face and neck, limbs, wrists; 1%	Yes	No	No	Yes, father	No	Yes, partial
8, male	38	18	Nonsegmental	VI	Scalp, trunk; 2%	No	No	No	Yes, daughter	No	No, but spontaneous repigmentation
9, male	66	42	Nonsegmental	VI	Face and neck, scalp, trunk; 8%	No	No	No	No	No	No
10, male	18	5	Nonsegmental	VI	Face and neck, scalp, trunk	Yes	No	Yes, Hashimoto thyroiditis	Yes, brother	Yes, autoimmune thyroiditis	No
11, female	21	6	Focal then nonsegmental	VI	Face and neck, armpits; 1%	no	No	no	No	No	No
12, male	54	5	Nonsegmental	VI	Trunk, limbs; 22%	No	No	Yes, diabetes type 1	No	Yes, Hashimoto thyroiditis	No
13, female	14	4	Nonsegmental	VI	Face and neck, trunk, limbs; 6%	No	No	No	No	No	No
14, female	22	2	Nonsegmental	VI	Face and neck, trunk; 1%	No	No	No	No	No	No
15, male	54	18	Nonsegmental	VI	Face and neck, scalp, trunk; 5%	No	No	No	No	No	No
16, male	44	22	Nonsegmental	VI	Face and neck, scalp, trunk, limbs	No	No	No	Yes, son	Yes, diabetes type 1	No
17, female	43	2	Nonsegmental	VI	Trunk, limbs and buttocks	No	No	No	No	No	No
18, male	33	6	Nonsegmental	VI	Face and neck, scalp, trunk	No	No	No	No	No	No
19, female	19	5	Nonsegmental	VI	Face and neck, trunk, limbs	Yes	Yes, very few after 5 years of evolution	No	Yes, father	No	No
20, male	42	12	Nonsegmental	VI	Face and neck, scalp, trunk	No	No	No	No	No	No
21, male	40	22	Nonsegmental	VI	Face and neck, trunk	No	No	No	No	No	No

Table 1 (continued)

Patient, sex	Age (years)	Disease duration (years)	Type of distribution	Phototype	Site of lesions; total body surface area involved	Depigmentation on scars/ Koebner phenomenon	Presence of concomitant depigmented macules	Personal history of other autoimmune diseases	Familial history of vitiligo	Family history of other autoimmune diseases	Response to treatment
22, male	45	23	Nonsegmental	VI	Face and neck, scalp, trunk	No	No	No	No	No	No
23, male	32	25	Nonsegmental	VI	Face and neck, scalp, trunk	No	No	No	No	No	No
24, male	42	5	Nonsegmental	VI	Face and neck, scalp, trunk, limbs; 3%	No	No	No	No	No	No

Table 2 Descriptive characteristics of 24 patients with hypochromic vitiligo

Characteristic	n
Sex	
Male	14
Female	10
Age at consultation (years), mean (range)	35·4 (8–66)
Disease duration (years), mean (range)	12·3 (1–42)
Family history of vitiligo	
Yes	5
No	19
Family history of autoimmune diseases	
Yes	4
No	20
Personal history of autoimmune diseases	
Yes	5
No	19
Anatomical sites involved	
Head and neck	20
Scalp	14
Trunk	20
Limbs	13
Hands and feet	2
Koebner phenomenon	
Yes	4
No	20
Presence of depigmented macules	
Yes	5
No	19
Response to conventional treatment	
Yes, complete	0
Yes, partial	3
No	21
Episode of spontaneous repigmentation	
Yes	1
No	23

the patients in this case series were found to have hypopigmented macules in nonseborrhoeic areas, mainly the trunk and limbs. The presence in a few patients of associated completely isolated depigmented macules is also suggestive of vitiligo. Finally, in all examined biopsy specimens there was an absence of signs of inflammation, absence of spongiosis localized to the ostia or upper infundibula of the hair follicles, no evidence of *Pityrosporum* (*Malassezia*) yeast spores in the stratum corneum, and negative periodic acid–Schiff staining. All these elements argue against the diagnosis of seborrhoeic dermatitis and tinea versicolor. With regard to leprosy, this diagnosis was easily ruled out as there was no sign of hypoesthesia, with no clinical infiltration of the affected skin in these patients. In addition, the clinical course of the disease was inconsistent with leprosy, and results from biopsies showed no polymorphous infiltrate – especially macrophages in the upper and mid dermis or around neurovascular bundles and sweat glands – and no infiltrated nerves in the subcutaneous fat.

Some hypopigmented lesions located on the trunk were clinically consistent with mycosis fungoides-type CTCL at early

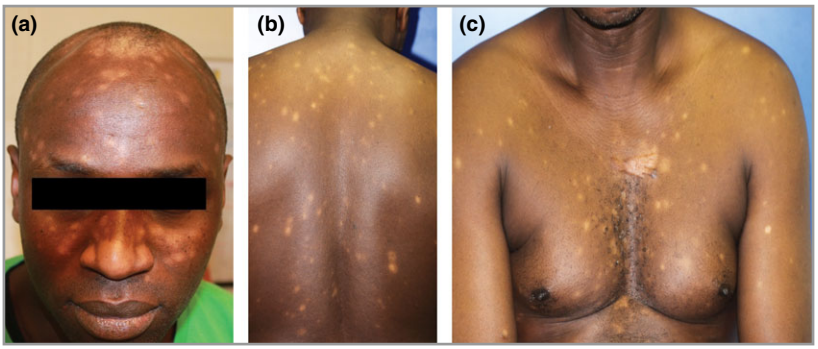

Fig 1. (a) Hypopigmented macules distributed on the face on seborrhoeic areas. Note the achromic macules on the scalp in a 37-year-old man. (b, c) Hypopigmented macules of the trunk, back and arms in the same patient.

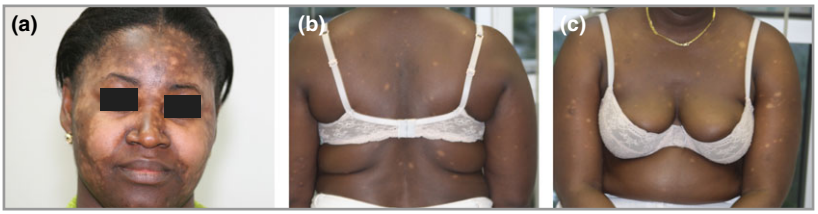

Fig 2. (a) Hypopigmented macules distributed on the face on seborrhoeic areas. Note the achromic macules on the scalp in a 44-year-old woman. (b, c) Hypopigmented macules of the trunk, back and arms in the same patient.

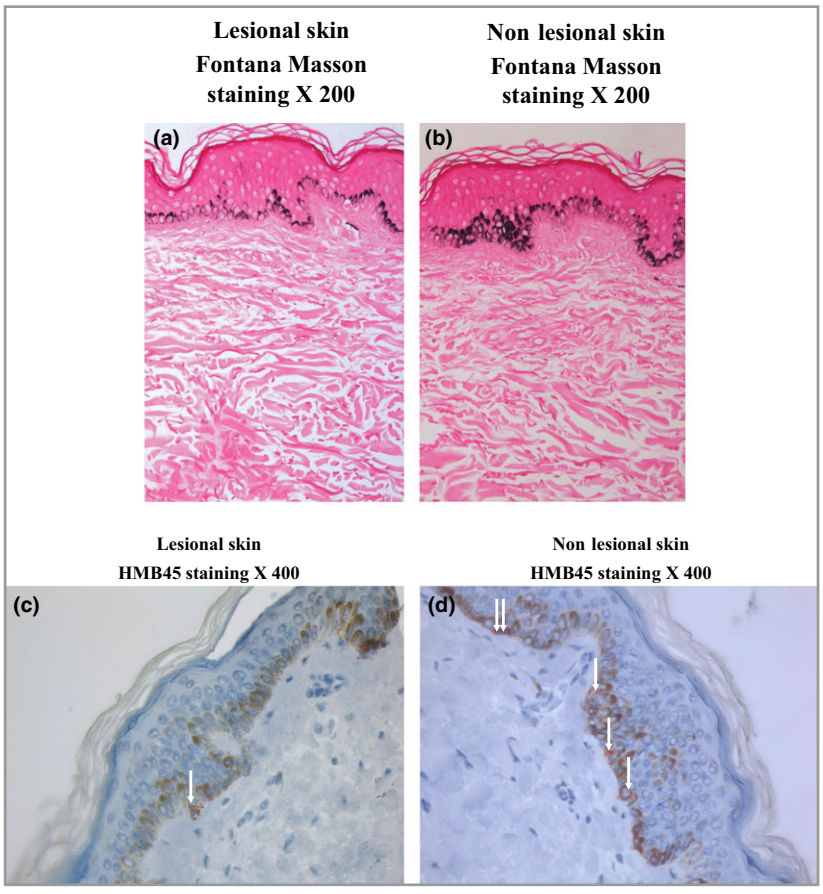

Fig 3. Fontana–Masson staining (×200) (a) in a hypopigmented macule and (b) in the same patient in surrounding nonaffected skin. Note the irregular decrease of pigmentation in lesional skin. (c) Immunostaining using HMB45 antibody (×400) on lesional hypopigmented skin. (d) Immunostaining using HMB45 antibody (×400) in the same patient in surrounding unaffected skin. Note the difference in the number of immature melanosomes featuring melanocytes marked in red by HMB45 staining.

stages. However, the facial seborrhoeic involvement is uncommon in that disease, and the stability of the lesions over time (> 10 years in 10 patients) and their unique localization argue against mycosis fungoides. Moreover, no atypical lymphocytic infiltrate with band-like disposition in the upper dermis, or foci of epidermotropism were observed in any biopsies.

Other causes of hypopigmentation, such as pityriasis versicolor, pityriasis lichenoides chronica and atopic dermatitis, were easily ruled out because of the clinical and histological patterns.

Hypochromic vitiligo appears to be a clinical entity with specific patterns. Hence, the seborrhoeic face and neck

involvement associated with hypopigmented macules of the trunk seems to be a hallmark of the entity, seen in most of the patients. Strikingly, we report the condition exclusively in dark-skinned individuals, although we cannot exclude that the condition may exist in fair-skinned people in whom hypopigmentation is less prone to be seen.

The presence of completely depigmented macules may help the diagnosis. However, this clinical sign is rarely observed. In the last consensus conference for vitiligo classification, hypochromic vitiligo/vitiligo minor was considered part of NSV.[3] Therefore, all patients with hypochromic vitiligo may potentially develop depigmented lesions. Our finding that 21% of the patients with hypochromic vitiligo have an associated autoimmune disease is consistent with previous reports of NSV.[7,8] Indeed, in our series three patients had concomitant autoimmune thyroiditis and two patients had either diabetes type 1 or urticaria. Additionally, a family history of vitiligo was also present in 21% of patients in our series.

Histological examination remains mandatory to exclude differential diagnoses that should be ruled out, especially hypopigmented mycosis fungoides. Because of the absence of typical signs of inflammation, biopsies should be taken from both lesional and surrounding healthy skin to allow comparison of the melanocyte and melanin distribution. One of the striking histological signs in hypochromic vitiligo is the apparently normal aspect of histology with a decrease of both melanin and the number of melanocytes. Contrarily to the hypomelanotic lesions of unstable classical vitiligo, the CD8 T-lymphocytic infiltrate is not prominent and melanophages are rarely present in the dermis of hypochromic vitiligo.[5] In some cases of postinflammatory hypopigmentation, characteristic histological features of the original disease may not be found; however, this decrease in the number of melanocytes compared with surrounding healthy skin is the pathognomonic histological sign of hypochromic vitiligo, as a decrease in the number of melanocytes is not observed in postinflammatory hypopigmentation.[9] Comparative biopsies of hypopigmented lesions and healthy surrounding skin with melanocyte staining are thus sometimes mandatory to rule out differential diagnoses. Surprisingly, response to treatment is poor in hypochromic vitiligo, whereas the incomplete depigmentation with persistence of melanocytes might argue for a better therapeutic response.

In conclusion, we herein report and delineate the clinical and histological spectrum of a type of vitiligo that we propose to name hypochromic vitiligo, because of the partial defect in pigmentation with mostly hypopigmented lesions. This is a rare form of NSV that has been very sparsely reported, and the disease seems to be limited to dark-skinned individuals. Clinicians should be aware of this unusual, but not exceedingly rare, and misleading form of vitiligo. Immunological studies may help to complete the delineation of this new entity. Based on our series, its most consistent clinical features are the following. (i) Hypopigmented seborrhoeic face and neck involvement associated with hypopigmented macules of the trunk and scalp in dark-skinned patients. (ii) Few or absence of completely depigmented lesions despite a clinical course over several years. (iii) Decrease of pigmentation and melanocyte number in lesional skin compared with surrounding healthy skin, without clear signs of inflammation and atypical lymphocytic infiltrate. (iv) Absence or poor response to conventional treatment of vitiligo. (v) Absence of leucotrichia.

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