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Chronic Actinic Damage in Pigmented and Depigmented Skin of Hispanic Patients with Vitiligo: Clinical and Histological Differences

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Abstract

Vitiligo is a common depigmentary disorder, with loss of epidermal Melanocytes as its hallmark. This absence of melanin hypothetically makes skin more susceptible to Chronic Actinic Damage (CAD) and skin cancer development. However, various studies have shown no increased incidence of skin cancer and some point to decreased actinic damage in skin with vitiligo. We studied 14 patients with vitiligo and analyzed clinical and histological markers of chronic actinic damage both in depigmented skin with vitiligo and in normal skin. We found fewer markers of clinical CAD in depigmented skin than in normally pigmented skin. When we analyzed histological, we found that in most patient's depigmented skin had increased hyperkeratosis, which is a previously reported finding, as well as atrophy, elastosis and telangiectasias. There are various hypotheses to explain these findings. Further studies are needed to establish if vitiligo provides protection against CAD, either by structural changes or a better immunosurveillance process in the skin affected by it.

Keywords: Chronic Actinic Damage (CAD); Non-Melanoma Skin Cancer (NMSC); Vitiligo; Depigmented skin; Pigmented skin

Introduction

Vitiligo is the most common pigmentary disorder, with a prevalence of 0.5-1% in the world population. Almost half of patients present with the disease are below 20 years of age. Both sexes are affected equally and apparently there are no differences in prevalence according to skin type and race [1].

The pathologic hallmark is a loss of epidermal melanocytes. An inflammatory infiltrate can be found or not, especially at the margins of the depigmented area. The pathophysiology is still debated, but involves immune factors, oxidative stress or a sympathetic neurogenic disturbance. Some genes have been associated with vitiligo, either in isolation or as part of an autoimmune diathesis [1].

Melanocytes have several functions, among which is the absorption of Ultraviolet Radiation (UVR). The skin is the main barrier to external environment and relies on melanocytes to provide photoprotection and thermoregulation by producing melanin. Pigmentation protects skin by straightforward shielding by melanin, but also because melanocytes survive considerable oxidative stress. The degree of pigment production manifests as skin phototype, and is the most useful predictor of skin cancer risk [2]. So the degree of protection against Chronic Actinic Damage (CAD) depends on the cumulative dose of sunlight versus the efficacy of the anti-oxidant defense mechanisms of the skin. This protective role of melanin is supported by the lower susceptibility to actinic damage and skin cancer in darker phototypes compared to lighter ones [2-5]. This is further supported in African albinos who experience high incidences of actinic damage and Non-Melanoma Skin Cancer (NMSC) during their entire lifetime [6].

Skin with Chronic Actinic Damage (CAD) is characterized by wrinkling, telangiectasias, mottled pigmentation, atrophy, laxity, pseudoscars, purpura and premalignant or malignant neoplasms. Histological changes of chronic epidermal actinic damage are variable thickness of the stratum corneum, with areas of severe hyperplasia besides atrophy, some degree of nuclear atypia in melanocytes and keratinocytes [7-10]. There are different qualitative and quantitative methods for determining actinic damage but no standardized, reproducible method has been proposed [11-13].

Since patients with vitiligo have areas without melanocytes and consequently without pigment, we would expect these persons to have an increased risk of CAD and NMSC. However, several reports point to the exact opposite. Several studies have shown low incidence of skin cancer in patients with vitiligo [14,15]. Moreover, a lot of patients with vitiligo have used phototherapy or photochemotherapy for their disease, and one would expect this group to have a much higher incidence of NMSC. But proportionally to the high prevalence of vitiligo, there are few reports of increased skin cancer in patients with vitiligo even after psoralen and UVA (PUVA) therapy [16-25]. In a recent study, no increased risk for photosensitivity disorders and no signs of increased CAD in the skin of patients with vitiligo were found [14].

One hypothesis for these findings is that patients with vitiligo perform better sun protection measures due to increased risk of burning, but even in remote areas where patients are not using sunblocking substances, a lack of actinic keratosis or NMSC has been reported. Another study proposed that the stratum corneum in the skin with vitiligo was thicker and this could protect the depigmented skin from UV radiation [26].

All of these studies trying to establish a connection between

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depigmented skin with vitiligo and CAD have been done in caucasian populations. In this study, we examined a group of hispanic patients with skin phototypes III-V and vitiligo to describe clinical and histological markers of CAD in pigmented and depigmented skin.

Materials and Methods

We selected 14 patients (7 males and 7 females) with vitiligo from our outpatient dermatology clinic. All patients authorized the study and signed a consent form. All patients were subjected to a complete physical examination and clinical markers of CAD were intentionally searched for and evaluated (Table 1). Two 4-mm punch biopsies were taken under local anaesthesia from sun exposed skin; one biopsy was from depigmented skin and the other one from normal skin. Both biopsies were processed, stained with hematoxilin and eosin and silver stain and reviewed by a dermatopathologist, who intentionally searched for and evaluated histopathological signs of CAD (Table 2).

According to the clinical and histopathological signs that were evaluated, each patient received a score and was categorized in one of four grades of CAD depending on the score (0 points=none, 1-5 points=mild, 6-10 points=moderate, ≥ 11 points=severe).

Results

The patients' demographic data are shown in Table 3. The mean age was 48.4 years. All patients had skin phototypes III to IV. The mean duration of the disease was 21.1 years. None of the patients had a history of sunburns.

Clinical chronic actinic damage (CAD)

In normally pigmented skin, 1 patient (7%) had no markers of, 11 (78%) had mild and 2 (14%) had moderate damage; average score was 4 points (56/14).

In depigmented skin, 2 patients (14%) had no markers of, 11 (78%) had mild, and 1 (7%) had moderate damage; average was 1.85 points (26/14).

In Figure 1, we can see the distribution of the score for clinical CAD in each patient's normally pigmented skin compared with depigmented skin. In Figure 2, we can see the distribution of the summed score for all patients in both types of skin.

Clinical marker	Score
Xerosis	1
Freckles	1
Lentigines	1
Guttate hipomelanosis	1
Persistent hyperpigmentation	1
Fine wrinkles	1
Deep wrinkles	1
Stellate pseudoscars	1
Elastosis	1
Loss of elasticity	1
Telangiectasias	1
Venous lakes	1
Purpura	1
Comedones (Favre-Racouchot)	1
Actinic keratoses	10
Non melanoma skin cancer	10
Melanoma	10

0 points=no photodamage, 1-5 points=mild photodamage, 6-10 points=moderate actinic damage, ≥ 11 points=severe actinic damage

Table 1: Clinical markers of Chronic Actinic Damage (CAD).

Histological marker	Score
Hyperkeratosis	1
Acanthosis	1
Lentigines	1
Epidermal atrophy	1
Epidermal hyperpigmentation	1
Fibroblast hyperplasia	1
Nodular elastosis	1
Diffuse elastosis	1
Ephelides	1
Lentigines	1
Telangiectasias	1
Venous lakes	1
Purpura	1
Comedones	1
Actinic keratoses	10
Non melanoma skin cancer	10
Melanoma	10

0 points=no actinic damage, 1-5 points=mild actinic damage, 6-10 points=moderate actinic damage, ≥ 11 points=severe actinic damage

Table 2: Histopathological markers of Chronic Actinic Damage (CAD).

	n (%)
Sex	
Female	7 (50%)
Male	7 (50%)
Age (years)	
20-29	2 (14.2%)
30-39	3 (21.4%)
40-49	3 (21.4%)
50-59	3 (21.4%)
+60	3 (21.4%)
Phototype	
III	2 (14.2%)
IV	9 (64.2%)
V	3 (21.4%)
Evolution of vitiligo (years)	
5-9	1 (7%)
10-15	5 (35.7%)
16-20	3 (21.4%)
21-25	2 (14.2%)
26-30	3 (21.4%)
History of sunburns	
Yes	2 (14.2%)
No	12 (86%)
History of photosensitivity reactions	
Yes	1 (7%)
No	13 (93%)

Table 3: Demographic characteristics of the patients with vitiligo.

Histological chronic actinic damage (CAD)

In normally pigmented skin, 7 patients (50%) had no markers of and 7 (50%) had mild damage; average was 0.64 points (9/14).

In depigmented skin, 4 patients (28%) had no markers of and the rest (72%) had mild damage; average was 1.85 points (20/14).

In Figure 3, we can see the distribution of the score for histological chronic actinic damage in each patient's normally pigmented skin *vs* depigmented skin. In Figure 4, we can see the distribution of the summed score for all patients in both types of skin.

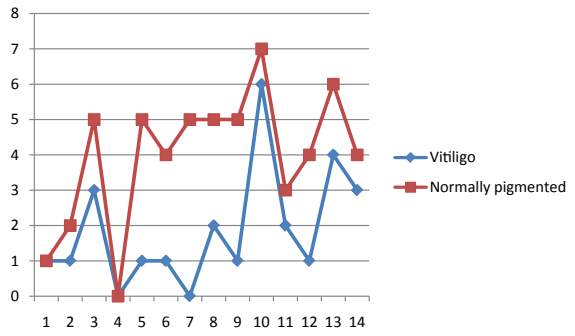

Figure 1: Comparison between each patient's degree of clinical chronic actinic damage in depigmented skin with vitiligo *vs* normally pigmented skin.

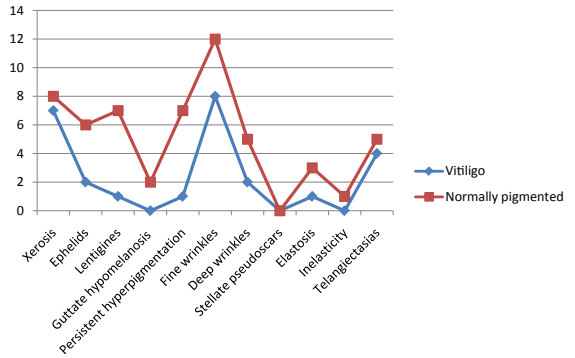

Figure 2: Distribution of the overall clinical chronic actinic damage score found on all patients, comparing depigmented skin with vitiligo *vs* normally pigmented skin.

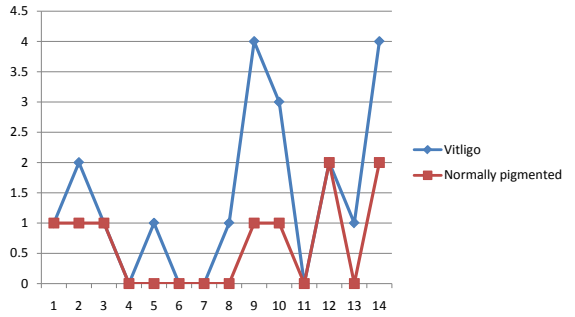

Figure 3: Comparison between each patient's degree of histological chronic actinic damage in biopsies of depigmented skin with vitiligo *vs* normally pigmented skin.

Discussion

In this study, we analyzed clinical and histological findings suggestive of CAD in patients with Fitzpatrick´s skin phototype III to IV who also had depigmented skin affected by vitiligo. We found several interesting results.

First, there were fewer findings of clinical CAD in depigmented skin with vitiligo than in normally pigmented skin (Figure 5). This is compatible with previous reports where large cohorts of patients with vitiligo have been found to have a low incidence of skin cancer. Calanchini-Postizzi and Frenk studied 23 patients with longstanding vitiligo, and only found 3 actinic keratoses in sun-exposed vitiligo skin [15]. Similarly, there are very few reports of patients with vitiligo developing a squamous cell carcinoma after PUVA therapy [16-19] and one developing a keratoacanthoma after therapy with narrow band UVB (NB-UVB) [25].

Large cohort studies have followed patients with vitiligo and phototherapy and have found no evidence of NMSC or melanoma [20-23]. The largest series up to now is by Westerhof and Schallreuter [24], who studied 2500 patients with vitiligo without finding any cases of skin cancer.

One of the hypothesis that has been proposed for a lower incidence of CAD is that patients with vitiligo perform better photoprotection measures that healthy individuals and this could be the reason of lower actinic damage manifestations [26]. But patients with vitiligo in Tanzania who cannot use sunblocking substances or physical measures do not have any evidence of actinic keratosis or NMSC, as Nordlund recently reported [27].

When we analyzed histological signs, we found that in most patients, the depigmented skin with vitiligo had slightly more markers of CAD than normal skin. The change that predominated in the biopsies of skin with vitiligo while none of the biopsies of normally pigmented skin had, was hyperkeratosis, which is a previously reported finding (Figures 6 and 7). Everett [28] observed hyperkeratosis of the stratum corneum in the skin with vitiligo, and proposed that this could protect the depigmented skin from UV radiation [28]; nonetheless, the photoprotecting capacity by unit of thickness was lower than in normal skin [26].

Besides hyperkeratosis, the other markers that were found to

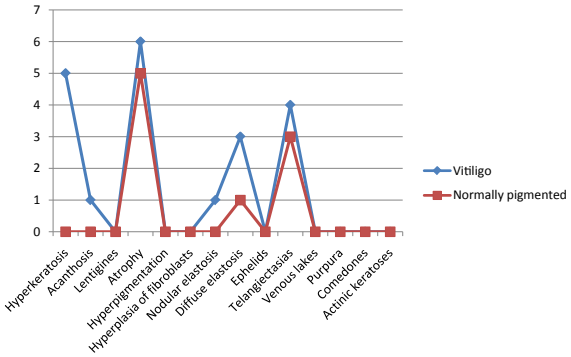

Figure 4: Distribution of the overall histological chronic actinic damage score found on all patients, comparing depigmented skin with vitiligo *vs* normally pigmented skin.

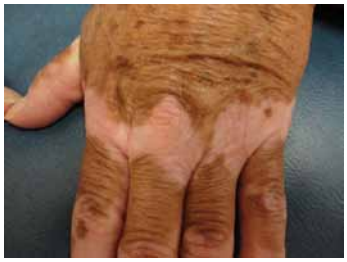

Figure 5: Chronic actinic damage is clinically more evident in pigmented skin: atrophy, fine and coarse wrinkling.

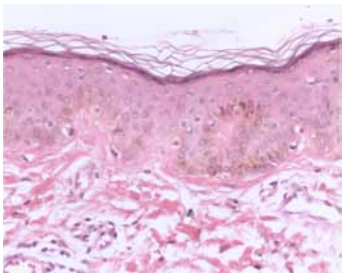

Figure 6: Biopsy of pigmented skin. No histological markers of chronic actinic damage.

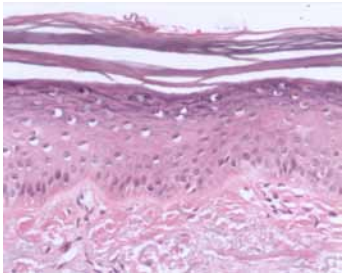

Figure 7: Biopsy of the same patient, depigmented skin. Marked hyperkeratosis and elastosis.

be more frequent in the biopsies of skin with vitiligo were: atrophy, elastosis and telangiectasias. However, our group of patients is not large and so the differences detected in 1 or 2 patients are not significant.

Previous studies have found decreased signs of CAD in skin with vitiligo as Schallreuter et al. [14], who found no difference in histological signs of CAD in biopsies of sunexposed normally pigmented and depigmented skin, although skin with vitiligo had persistent oxidative stress by millimolar amounts of H_2O_2. Their results support that individuals suffering from vitiligo must be protected against CAD by mechanisms other than melanin and stratum corneum thickening [14].

Calanchini-Postizzi and Frenk [15] performed a study comparing skin with vitiligo and normal skin, and found no evidence of an increase in CAD in the skin without melanin.

Another comparison between patients with vitiligo and healthy controls reported fewer sunburn cells in the former group [29].

Schallreuter et al. studied the expression of epidermal p53 in patients with vitiligo and found an increased upregulation of the wild type p53 protein in comparison with healthy controls. This increase in this tumor suppressing gene could play a role in the low incidence of skin cancer in these patients [30].

This is the first study that has analyzed both clinical and histological CAD in hispanic patients, who have darker phototypes, affected by vitiligo. This is an observational, descriptive study with a limited number of patients, so a statistical analysis is impossible. It is difficult to reach conclusions based on the differences detected in our study. However, we can learn from these findings that show a distinct trend which has been described before.

Our findings as well as previously reported analyses all together show evidence that there are several factors playing a role in possibly a better immunosurveillance in depigmented skin with vitiligo or better DNA-repairing mechanisms. Further research in the subject is needed as the etiology of these apparently contradictory findings could be of use in developing new immunotherapy options for melanoma.

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