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Original Article

Monobenzone is still the main culprit of chemical vitiligo

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Abstract

Background Chemical vitiligo is a special variant of vitiligo where the destruction of melanocytes occur at the basal layer of the epidermis and it is initiated by phenolic chemicals either part of industrial contamination of workers or during the course of using monobenzone as a topical depigmenting agent.

Objective To report and evaluate all patients with chemical vitiligo and to delineate the different triggering factors.

Methods This is a case series descriptive study where all patients with chemical vitiligo were gathered during the time from 2014-2021 years. A careful history and full examination were carried including the history of facial chemical exposure and other triggering offending agents. Woods light examination was applied to confirm the clinical diagnosis. All patients with facial leukoderma were treated by topical methoxsalen 1% lotion followed by sunlight exposure (3 times weekly) combined with topical mometasone furoate ointment 0.1% daily and pimecrolimus cream 1% at night for two months.

Results Thirty-two patients were seen with chemical vitiligo, their ages ranged from 20 -50 with a mean of 35 years, with twenty-three (71.8%) females and nine (28.2%) males. Topical monobenzone was applied for 18 (56.25%) patients for the treatment of facial pigmentation mainly for melasma and some cases for lichen planus actinicus. The white areas appeared after 3-6 months of monobenzone cream use. While six (18.75%) cases followed black hair dying and four (12.50%) patients with unknown causes as used multiple cosmetic procedures. Also, one (3.12%) patient gave a history of using rubber sandals that induced contact dermatitis that was followed by chemical vitiligo on the dorsa of both feet. One (3.12%) female patient had linear depigmentation along the leg that followed a triamcinolone intralesional injection of the heel. In addition, one (3.12%) patient had a history of laser used for melasma. While in one (3.12%) patient, his problem followed multiple intralesional triamcinolone injections for melasma. All 31 patients with facial leukoderma showed confetti-like depigmentation of the face but no distant metastatic leukoderma was revealed. These patients with facial leukoderma responded very well to their treatment.

Conclusion Chemical vitiligo is still a medical problem that is commonly induced by the topical application of monobenzone as therapy for melasma. Black hair dying was reported for the first time as a cause of chemical vitiligo. These patients often present with confetti-like depigmentation.

Key words
Vitiligo; Chemical vitiligo; Monobenzone; Black hair dye.

Introduction

Vitiligo is one of the common dermatological conditions, affecting around 2% of the population worldwide.[1-3] presents usually with well-circumscribed, hypopigmented, white macules or patches. Vitiligo usually occurs due to acquired autoimmune destruction of

melanocytes, most often involving the face, and dorsum of the hand's areas most exposed to UV radiation.[2,4,5] The pathogenesis of vitiligo is affected by genetic and environmental contributing factors.[6] The study carried out by Sharquie *et al*. described a new hypothesis regarding follicular vitiligo formation which suggested that the loss of melanocytes involves the fixed segment of hair follicle mainly the infundibulum and appears as tiny follicular depigmented macules, this follicular depigmentation would coalesce together to form the ordinary patches of vitiligo.[7-9] Many published studies discussed the risk of vitiligo is attributed to genetic factors in 80% of cases while in (20%) is caused to environmental stimuli.[10,11] Many similar published studies have been carried out to discuss another process of the mechanism of destruction of melanocytes is initiated by Oxidative stress.[12]

Dell'anna *et al*. hypothesized that Melanocytes respond to oxidative stress by releasing reactive oxygen species (ROS). This causes an extensive change in the antioxidant system: An imbalance between pro-oxidants (superoxide dismutase, malondialdehyde, xanthine oxidase) and enzymatic and nonenzymatic antioxidants in the skin and the blood.[13] Many similar studies have been done suggesting reactive oxygen species can be elicited by both endogenous and exogenous stressors. Examples of exogenous stimuli are ultraviolet (UV) radiation and monobenzone depigmenting agents.[14] Monobenzone has been acting to induce the release of melanosomal-related antigen-containing exosomes following the overproduction of ROS from melanocytes.[15]

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Many published studies have been carried out to consider the term 'chemical vitiligo' indicating the possible relationship between chemical leukoderma and vitiligo, which has been supported recently by other authors like Harris *et al*. to designate the term 'chemical-induced vitiligo.[6,16,17] Hydroquinone is a commonly prescribed drug for melasma, post-inflammatory hyperpigmentation, and various other indications. Many published studies reported adverse effects of hydroquinone including irritant contact dermatitis and exogenous ochronosis. In rare circumstances, it can lead to permanent depigmentation of the skin which manifested clinically as confetti-like hypopigmented and depigmented macules. It was first reported by many studies to appear with mono benzyl ether of hydroquinone (MBEH) However, monomethyl ether of hydroquinone and native hydroquinone have also been reported by similar studies as causative factors for depigmentation.[18-22]

The mechanism of leukoderma could be related to the cytotoxic effects of hydroquinone on the melanocyte and may be dose-related as Sharquie *et al*. and similar studies hypothesized.[23-24] Many previous published reports suppose of hydroquinone-induced depigmentation were mostly among African, American, and Indian populations.[25,26]

In 1939, Oliver *et al*. first describe chemical leukoderma in a leather manufacturing company in those workers who used “acid-cured” rubber gloves. He hypothesized that MBEH, an antioxidant used in rubber manufacture was the culprit agent. In later decades, many similar published works have been carried out on occupational leukoderma caused by phenolic compounds.[18-20] Many published studies suggest other contributing chemicals are

paraphenylenediamine (PPD) and benzyl alcohol which is found in hair colors and rinses.[27,28] Household chemical exposure is also a major etiological factor and these chemicals include perfumes, deodorants, detergents, rubber sandals, and hair dyes. The mechanism of leukoderma after an intralesional or intra-articular corticosteroid injection is exactly unknown, but many similar studies have been done.[28,29] One theory carried out by Liang *et al*. suggests that the spread of corticosteroids after injection can lead to skin atrophy and linear loss of melanin pigment.[30] Another hypothesis supposes that corticosteroids may travel via the lymphatics or vasculature, leading to linear depigmentation, as hypothesized by Gaglio de Grecco *et al*.[31] It is also suggested that corticosteroids may lead to a decrease in the number of melanocytes or alter melanocyte function via cytokine or prostaglandin inhibition as reported by Venkatesan *et al*.[32] Laser-induced punctate skin depigmentation has been reported by many similar studies to cause by the Q-switched laser and the carbon dioxide laser.[33-35] The pathogenesis of laser-induced leukoderma has not been fully understood yet, Chan *et al*.[36] supposed two different mechanisms. First, excessive fluence may cause direct cellular destruction of melanocytes. Second, after multiple treatment sessions, the total cumulative dose with short intervals may also destroy the melanocytes, even if the fluence was not strong enough to cause phototoxicity directly.

Patient and Methods

Thirty-two patients complaining of chemical vitiligo gathered during the period from 2014-21 years were involved in this descriptive, observational, case-series. The study followed the principles of the Declaration of Helsinki. Consent forms were reported from all patients after discussing the nature of the study. The close-up photo was taken at the same place with a fixed distance and illumination. In addition, all included patients accepted the idea to share their photos in this present work.

A thorough history including the history of facial chemical exposure and other triggering offending agents with a well-established examination was done. Name, age, gender, residence, job, and past medical and drug history were taken from all patients. The type of lesions, duration of the disease, site, size, and number of lesions were also evaluated. Wood's lamp examination was applied to establish the diagnosis of leukoderma.

All patients with facial leukoderma were treated with topical methoxsalen 1% topical lotion followed by sunlight exposure (3 times weekly) combined with topical mometasone furoate ointment 0.1% daily and pimecrolimus cream 1% at night for two months.

Results

Thirty-two patients with chemical vitiligo were considered in the present work, with ages ranging from 20 -50 with a mean of 35 years, with 23 (71.8%) females and 9 (28.2%) males. The Types of contributing factors for chemical vitiligo in the studied patients were illustrated in **Table 1**.

Table 1 The types of contributing factors for chemical vitiligo in the studied patients.

Contributing Factor	*Number of Patients*	*Percentage of Total*
Topical Monobenzyl ether of Hydroquinone cream	18	56.25
Black hair dying	6	18.75
Intralesional injection of triamcinolone acetonide	2	6.25
Rubber sandals	1	3.12
Laser therapy	1	3.12
Multiple unknown cosmetic procedures	4	12.50

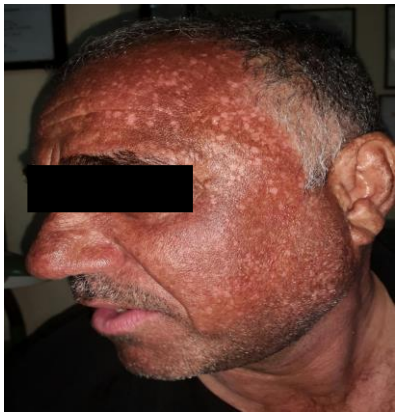

Figure 1 40-year-old male with confetti-like chemical vitiligo following monobenzone therapy.

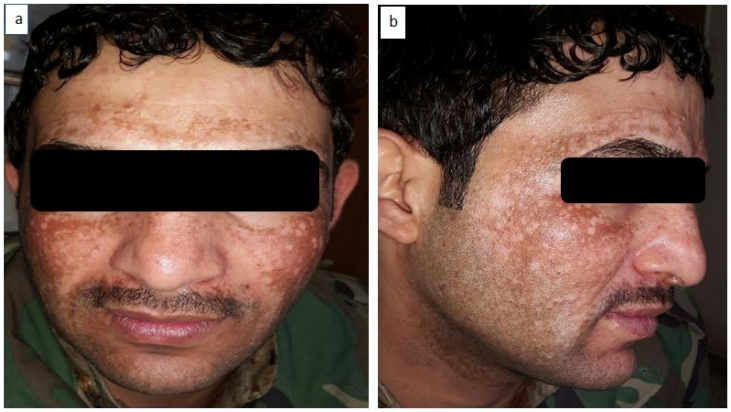

Figure 2 (a-b) 30-year-old male showing confetti-like depigmentation after monobenzone use for melasma.

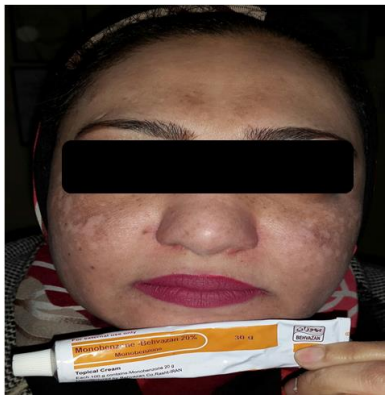

Figure 3 35-year-old female showing confetti-like after monobenzone therapy for melisma.

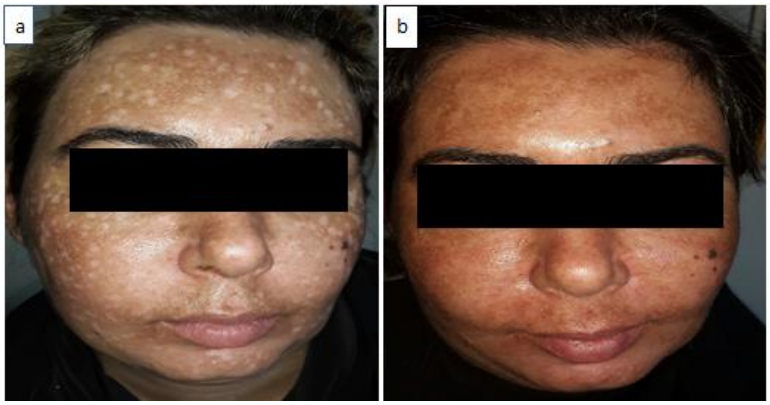

Figure 4 (a) 30-year-old female with chemical confetti vitiligo before therapy; (b) the same patient after therapy.

Topical monobenzone was applied for 18 (56.25%) patients for the treatment of facial pigmentation mainly for melasma and some cases of lichen planus actinicus. The white areas appeared after 3-6 months of monobenzone cream use **(Figure 1-4)**. While 6 (18.75%) cases followed black hair dying and 4 (12.50%) patients with unknown causes used multiple cosmetic procedures. Also, one (3.12%) patient gave a history of using rubber sandals that induced contact dermatitis that was followed by chemical vitiligo on the dorsa of both feet **(Figure 5)**. One female patient had linear depigmentation along the leg that followed triamcinolone intralesional injection of the heel **(Figure 6)**. In addition one (3.12%) patient had a history of laser used for melasma. While in one (3.12%) patient, his problem followed multiple intralesional triamcinolone injections for melasma. All 31 patients with facial leukoderma showed confetti-like depigmentation of the face but no distant metastatic leukoderma was revealed. There was initial itching in many patients. These patients with facial leukoderma responded to methoxsalen 1% topical lotion followed by sunlight exposure (3 times weekly) combined with topical mometasone furoate ointment 0.1% daily and pimecrolimus cream 1% at night for two months **(Figure 4)**.

Discussion

Chemical vitiligo cannot be easily differentiated from ordinary vitiligo but the confetti-like

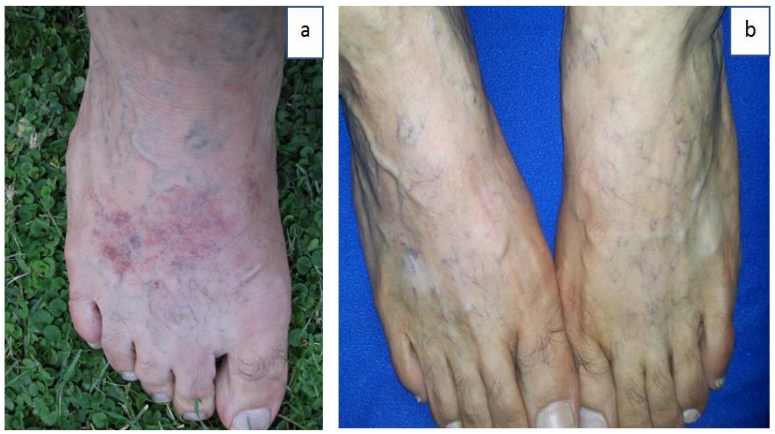

Figure 5 (a) 50-year-old male showing foot contact dermatitis after Indian rubber sandal; (b) The same patient showing rubber chemical vitiligo.

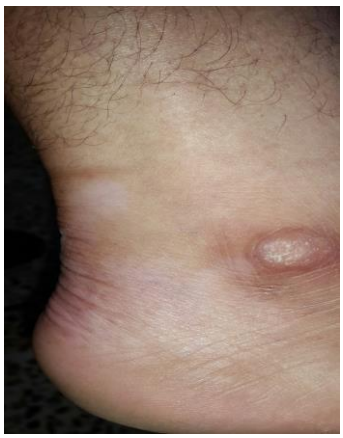

Figure 6 45year old female showing steroid leukoderma after injection of heel.

picture might be a helpful clue. The study carried out by Boissy *et al*. discussed the etiopathogenesis of chemical vitiligo which suggest it is mostly related to genetic factors, where melanocytes become more fragile and damaging by targeting agents. Contributing factors, are evident in chemical leukoderma in comparison to idiopathic vitiligo, initiate programmed cell death, or apoptosis of melanocytes as reported.[37]

Another theory carried by Kroll *et al*. suggested that the production of radical oxygen species by Tyrosinase-related protein-1 (Tyrp1), through catalytic conversion of chemicals, to prevent cell death, this oxidative stress triggers the activation of cellular free-radical scavenging pathways. The melanocytic genetic inability to respond and/ or tolerate oxidative stress may support the pathogenesis of chemical leukoderma.[38]

Both studies suggested other theories for the pathogenesis of chemical vitiligo where increased TNF-related apoptosis-inducing ligands (TRAIL) death receptor expression and heat shock protein (HSP) consider important aspects in the initiation of chemical vitiligo and its spreading by systemic auto-immunity. Melanocyte exposed to 4-tertiary butyl-phenol (TBP) induces elevated TRAIL expression. TRAIL expression is strongly positive even in peri-depigmented areas.[37,38]

Similar studies have been done and supposed Dendritic cell (DC) effector functions also take an important role in the generalization of leukoderma. DC inactivation mediates stressed melanocytes by releasing heat shock protein (HSP70). DC function is partially inhibited by antibodies to TRAIL.[20,38]

In our study, chemical vitiligo remained limited to the site of exposure in all 32 cases, and no distant dissemination of the disease to outlying skin areas was reported. The patches in all cases were multiple involved commonly the face, females are affected more than males as reported in the literature.[17] This might be due to autoimmune conditions being more common in females and household commercial products used more than in males.

The initial itching was observed in some patients, it's mild in severity and not significant. Confetti-like depigmentation is characteristic of chemical vitiligo and is considered to be a clinical sign of highly active vitiligo as reported by the Harris *et al*. study[6] and seen in almost all

our cases. Monomethyl ether of hydroquinone, a compound used in the treatment of melasma also considered a possible cause of vitiligo as Sharquie *et al*. reported[24] presented clinically as confetti-like hypopigmentation and later with permanent depigmentation especially if used for long duration. Hair dying was reported for the first time as a cause of chemical vitiligo due to PPD and benzyl alcohol chemical compounds which are found in hair colors as described in the literature.[25,27] In one patient we reported chemical vitiligo due to Indian rubber sandals that he used preceded by contact dermatitis on the dorsa of both feet due to MBEH and phenolic compounds used in rubber industries.[18,26] This makes MBEH the main contributing factor for chemical vitiligo. Also in one patient, we reported linear depigmentation along the leg that followed triamcinolone intralesional injection of the heel and this might be due to linear loss of pigment, travel through lymphatics or vasculature, and decrease in the number of melanocytes as reported.[28-32] All our patients with facial leukoderma responded very well to topical methoxsalen lotion followed by sunlight exposure together with topical steroids and pimecrolimus cream. This put into consideration that treatment of chemical vitiligo is the same as ordinary vitiligo with a higher response rate.

Conclusion

Chemical vitiligo is still a medical problem that is commonly induced by topical application of monobenzone as therapy for melasma but other miscellaneous offending agents might be triggering factors such as using cosmetic agents like lasers and injections. Black hair dying was reported for the first time as a cause of chemical vitiligo. These patients often present with confetti-like depigmentation. Treatment of chemical vitiligo is similar to ordinary vitiligo after stopping the triggering agents. Monobenzone cream should be prohibited from use as it causes more harm to patients than its beneficial effects.

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