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Review article

CHEMICAL VITILIGO: A LITERATURE REVIEW

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Abstract

Chemical vitiligo is an underdiagnosed form of skin depigmentation caused by repeated chemical agent exposure, affecting both adults and children. Chemical vitiligo is also called chemical leucoderma, contact vitiligo, and/or occupational vitiligo. Most of the implicated chemical agents are derivates of phenol and catechol, which have melanotoxic effects in individuals with genetic susceptibility. The diagnosis of chemical vitiligo is based on the medical history and patch testing, as histopathology is usually inconclusive and cannot differentiate chemical from idiopathic vitiligo. Patients typically report multiple exposures to specific melanotoxic or depigmenting chemical substances, either in the household or at the workplace, followed by the appearance of diffuse confetti-like and/or pea-sized hypopigmented macules, usually on the face, hands, and feet. The widespread distribution of hypopigmented macules is often the result of sensitization, autotransfer, or heterotransfer of the chemical agent from the primary site of contact. Later, the clinical suspicion of chemical vitiligo can be confirmed with the patch test. Once the diagnosis is established, the patient should be advised to avoid the incriminated chemical agent. In some cases, when spontaneous repigmentation does not occur, additional treatments are recommended, such as ultraviolet B phototherapy, photochemotherapy, and topical immunosuppressants.

Keywords*:* chemical vitiligo, chemical leucoderma, skin hypopigmentation

Introduction

Chemical vitiligo is an acquired form of hypomelanosis, secondary to repeated exposure to melanotoxic or depigmenting chemical agents in genetically susceptible patients [1-2]. In the literature, this cosmopolitan disease is also referred to as *chemical leucoderma*, *occupational vitiligo*, and *contact vitiligo*[3]. However, the terms “chemical vitiligo” and “chemical leucoderma” are preferable to use, as “occupational” and “contact” can be misleading about the type of exposure. Occupational vitiligo refers specifically to exposure in the workplace, while contact vitiligo is limited to hypomelanosis at the site of contact with the agent [2].

Chemical vitiligo predominantly affects adult males and females, with a peak incidence between 20 and 40[4]. However, children under 12 should not be overlooked, especially in developing countries where household chemical exposure may occur. Most clinical cases of chemical vitiligo in pediatric patients are reported in India, while Western literature features only a handful of pediatric clinical cases [3]. The statistical discrepancies between Western and

developing countries are likely due to: 1. Lack of quality control in developing countries; 2. Limited medical awareness of chemical vitiligo; and 3. Underreporting of occupational diseases [1]. In contrast, the incidence of chemical vitiligo in developed countries has been decreasing, thanks to specific preventive measures, such as elimination, substitution, containment, and/or segregation of depigmenting chemical agents [4]. Both dark-skinned and light-skinned individuals are susceptible to chemical vitiligo [3].

When chemical vitiligo is suspected in a patient, some differential diagnoses should be excluded, such as idiopathic vitiligo, leucomelanoderma, post-inflammatory leucoderma, and Koebner phenomenon in vitiligo [1-2]. The diagnosis of chemical vitiligo relies primarily on the medical history and clinical features, as histopathology is inconclusive, and there are no definitive diagnostic tests aside from the patch test [1].

Material and methods

This article provides a review of chemical vitiligo. We conducted a systematic search of PubMed and Google Scholar for book chapters, original articles, review articles, and case reports on chemical vitiligo published in English between 2009 and 2025. The following search terms “chemical vitiligo” OR “chemical leucoderma were used.

Etiological and pathogenic aspects of chemical vitiligo

The significance of chemical vitiligo and its impact on quality of life has evolved considerably since 1939. Oliver *et al.* first reported on chemical vitiligo among workers in a leather manufacturing company exposed to monobenzyl ether of hydroquinone (MBH) [1]. In 1962, Russia documented chemical vitiligo in nearly half of the workers exposed to para-tertiary butylphenol (PTBP) and PTBP formaldehyde resins, with subsequent clinical cases reported in Japan, the USA, the Netherlands, and the United Kingdom [3]. In the 1990s, Taylor *et al.* reported skin hypopigmentation caused by the use of semi-permanent and permanent hair dyes, while in India, Pandhi and Kumar observed similar effects from decorative “bindi” adhesive on the Asian female’s forehead [1]. These findings made it clear that chemical vitiligo is not just an occupational skin disease but a cosmopolite one. In the past decade, additional depigmenting agents have been identified. In 2013, a Japanese skin lighting-creme caused an outbreak of vitiligo-like depigmentation in 16,000 of its users. The culprit agent was the creme active ingredient - rhodendrol [4-(4-hydroxyphenyl)-2-butanol] [5]. In 2016, Gozali *et al.* identified the depigmenting effects of dimethyl sulfate - a methylating agent primarily used in the pharmaceutical and chemical industries. The clinical case reported on two male workers, aged 36 and 51, who developed chemical vitiligo after repeated exposure to vapors of dimethyl sulfate [6].

As shown in Table 1, there are three major classes of depigmenting chemical substances. In most clinical cases, aromatic and aliphatic derivates of phenols and catechols are the incriminated depigmenting chemical agents. These melanotoxic agents can cause chemical vitiligo only in individuals with underlying genetic susceptibility. The genetic landscape associated with susceptibility to chemical vitiligo is still an unresolved mystery. Yet, certain genetic alterations in genes related to the function of innate (*NLRP1, IFIH1, CASP7, TICAM1, etc.*) and adaptive immunity (*CTLA4, CD80, HLA, GZMB, FOXP3*) may contribute to melanocytes fragility [2].

Melanocytes are neural crest-derived dendritic cells surrounded by approximately 34 keratinocytes in the epidermis. They are the primary site of melanin production, with the quality and quantity of melanin dependent on two enzymes: tyrosinase (TYR) and tyrosinase-related protein 1 (TYRP1) [8]. Phenol and catechol derivates have a hydroxyl side chain attached to a benzene ring, similar to the structure of the amino acid tyrosine [5]. As such, they act as tyrosine analogs, substituting the melanin precursor - tyrosine, in melanogenesis and

altering melanin production [9]. Another proposed pathogenic mechanism involves the production of chemical agent-derived reactive oxygen species (ROS) mediated by TYRP1 [1]. When oxidative stress surpasses the threshold of ROS scavenging pathways in fragile melanocytes, apoptosis is triggered, accompanied by an increase in tumor necrosis factor-related apoptosis-inducing ligands (TRAIL) and heat shock protein (HSP). Dendritic cells are another key player responsible for systemic autoimmune melanocyte destruction, activated by melanocyte-released heat shock protein (HSP70) [1].

Table 1. Major groups of melanotoxic depigmenting chemical agents [1-7]

Phenol and catechol derivates	Sulfhydryl	Miscellaneous agents
Monobenzyl ether of hydroquinone (MBH)	Cysteamine	Mercurials
Hydroquinone	Sulfanolic acid	Arsenic
p-tert-Butylcatechol (PTBC)	Cystamine dihydrohloride	Cinnamic aldehyde
p-tert-Butylphenol (PTBP)		PPD
p-tert-Amylphenol (PTAP)		Tretinoin
Additional phenol/catechol derivatives		Benzoyl peroxide
Monomethyl ether of hydroquinone (MMH)		Ammoniated mercury
Monoethyl ether of hydroquinone (MEH)		Azelaic acid
p-Phenylphenol		Fluorouracil
p-Octylphenol, p-Cresol		Carmustine

Clinical features and diagnosis

The diagnosis of chemical vitiligo is based on the patient's medical history and clinical features, as histopathology is often indistinguishable and overlaps with idiopathic vitiligo. Additionally, modern dermatology lacks standardized diagnostic tests, except for the patch test. Patients with chemical vitiligo often report repeated exposure to specific depigmenting chemical agents in their household and/or workplace. This history of repeated exposure is crucial for distinguishing chemical vitiligo from Koebner's phenomenon in vitiligo [1]. Multiple diffuse, confetti-like, or pea-sized macules can be seen at the site of primary contact with the chemical agent. However, they are usually seen on distant body parts as well. Hypopigmented macules can have either well-defined or ill-defined margins[4]. Over time, these hypopigmented macules can coalesce into larger hypopigmented patches[9]. The presence of numerous hypopigmented macules is often attributed to sensitization, autotransfer, and/or heterotransfer of the chemical agent [1]. These macules are typically widespread on the patient's face, hands, and/ or feet, while the scalp is a less commonly affected site in chemical vitiligo [3]. The clinical study by S. Ghosh and S. Mukhopadhyay published in 2009, which included 864 patients with chemical vitiligo, highlighted some key clinical and etiological aspects of chemical vitiligo [10]. Confetti-like macules were the most dominant diagnostic feature, seen in 89% of patients, with the face being the most commonly affected site (41.1%). As for the etiological factors, hair dyes (27.4%), deodorant and perfumes (21.6%), detergents, and cleansers (15.4%) were the most commonly implicated chemical agents. Additionally, 21.8% of patients reported itchiness as a symptom [10].

Patch testing plays a pivotal diagnostic role in cases with chemical vitiligo (see Fig.4). The test should be performed with a 2-10% solution of suspected chemical substances, and

read should be taken at 48 hours, 96 hours, after a month, and in some cases, even after 6 months. However, the lack of standardized solutions can make the patch testing unreliable, particularly in false negative cases [3]. Another valuable diagnostic tool that adds to the diagnosis of chemical vitiligo is the Wood's lamp (see Fig. 2). As a simple, non-invasive, and cost-effective diagnostic tool, the Wood's lamp can help detect early signs of chemical-induced skin hypopigmentation [9].

Once chemical vitiligo is diagnosed, patients are advised to avoid the chemical agent responsible for the skin hypopigmentation. Avoiding the chemical agent may lead to spontaneous repigmentation. However, in some cases, additional treatments are recommended. They may include narrow-band ultraviolet B (UVB) phototherapy, psoralen plus ultraviolet A (PUVA) photochemotherapy, topical immunosuppressants such as tacrolimus, and various surgical repigmentation techniques [11-12].

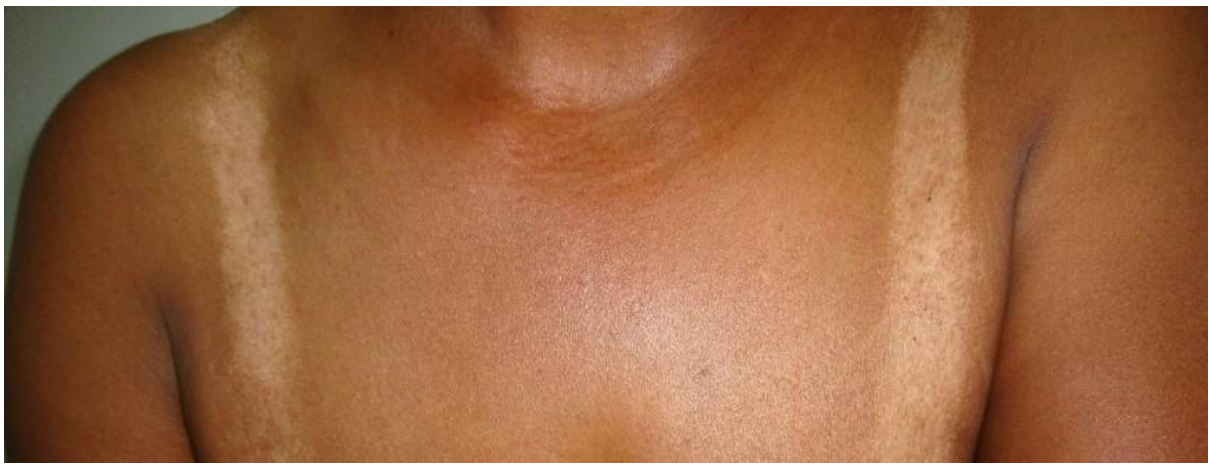

Fig. 1. Bra depigmentation due to mercapto-benzo-thiazole

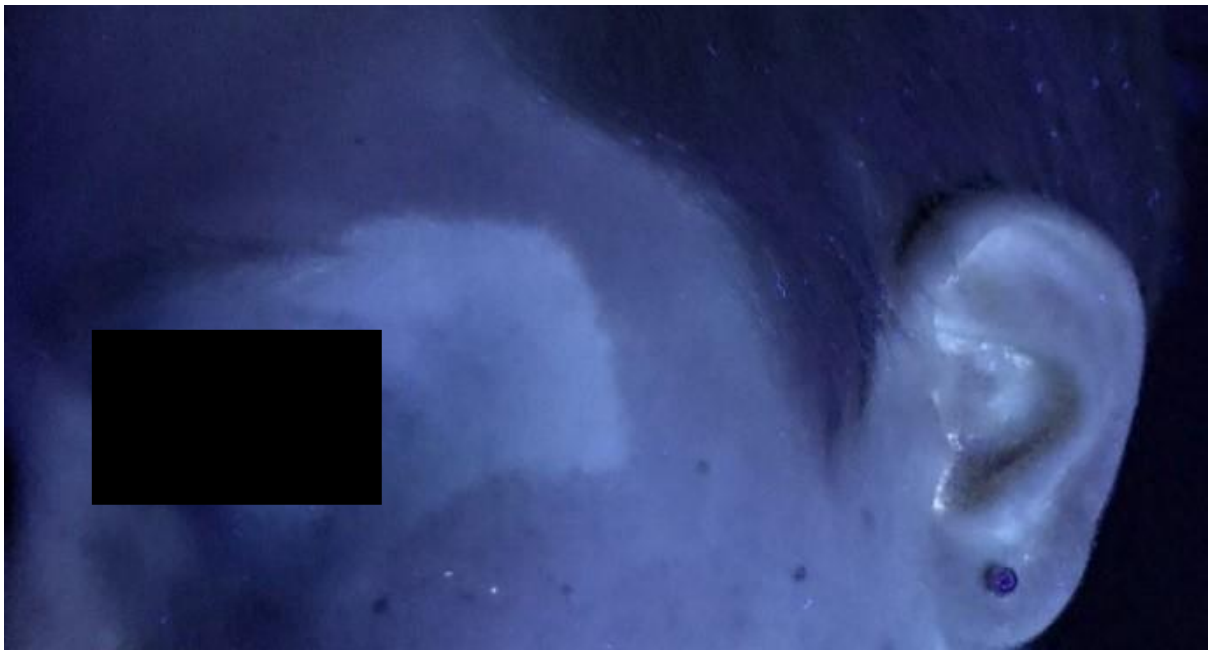

Fig. 2. Chemical vitiligo due to scuba diving mask

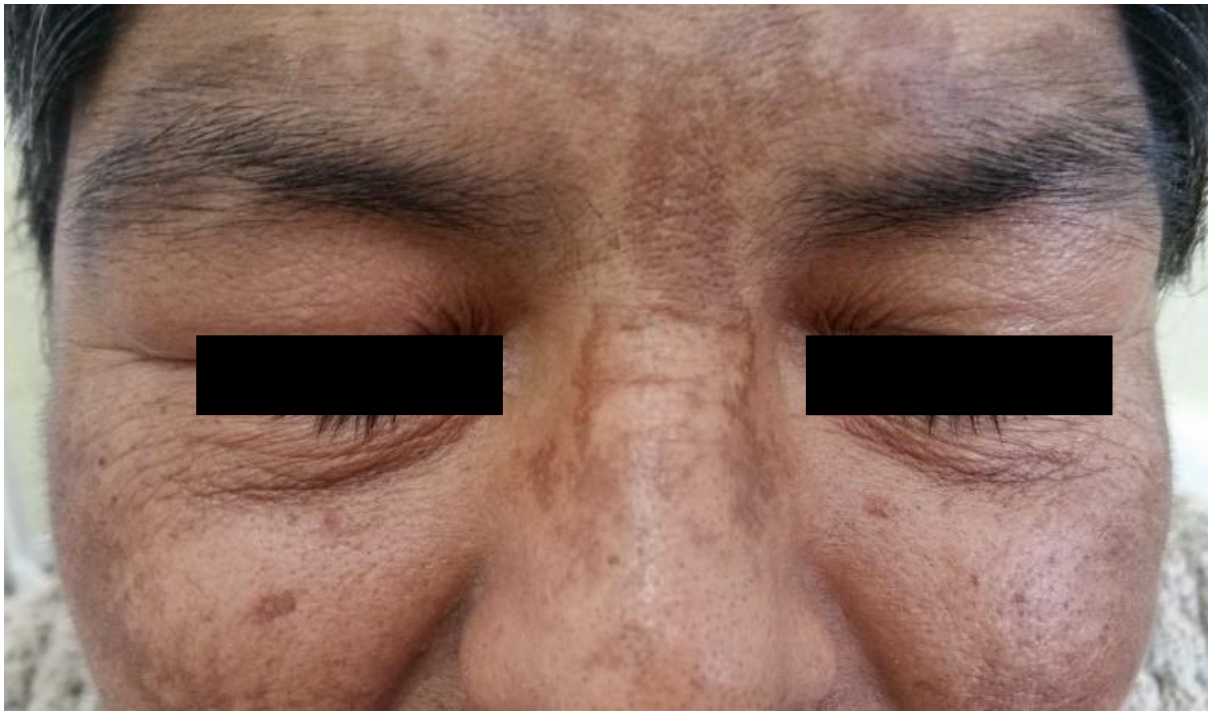

Fig. 3 Chemical leucoderma after use of a skin-lightening cream containing mercury in a patient with melasma

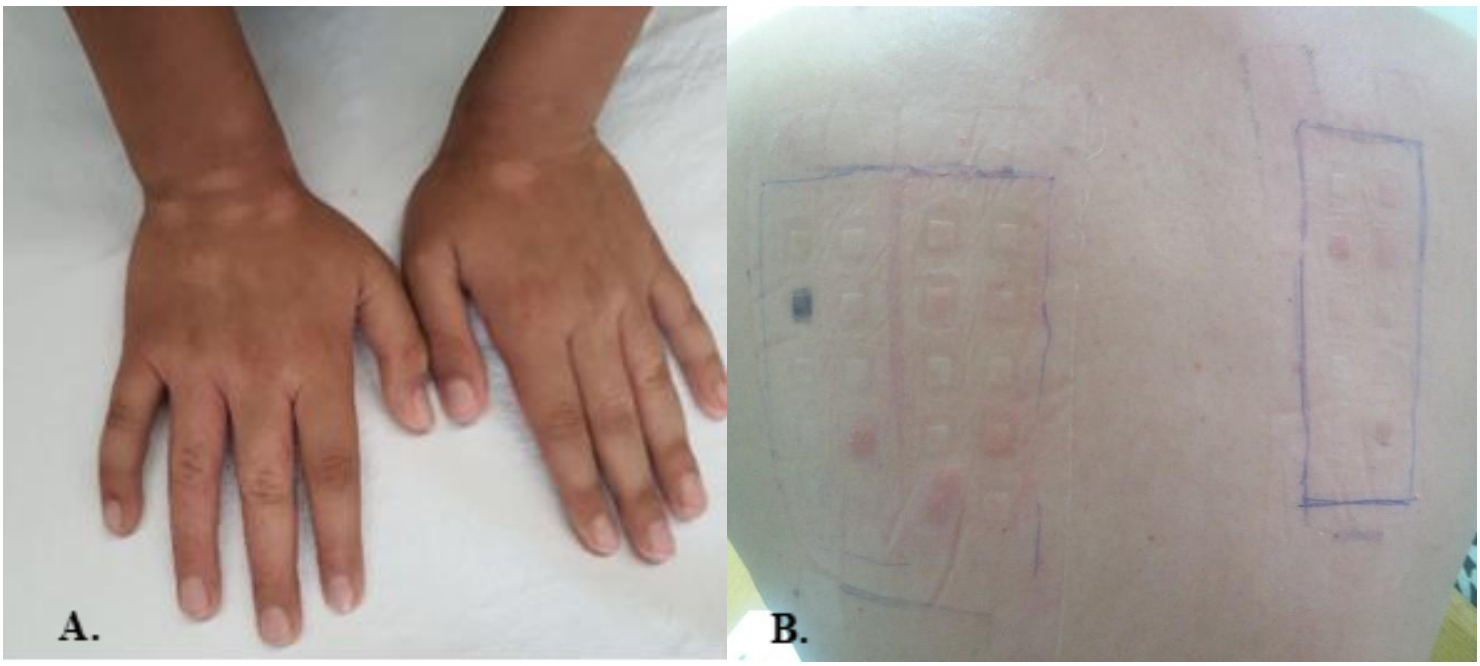

Fig. 4. A. Vitiligo-like depigmentation limited to the arms in a hairdresser; **B.** Patch testing in the same patient reveals polysensitization, confirming the diagnosis of allergic contact dermatitis.

Conclusion

Chemical vitiligo is a global yet often underdiagnosed skin disease linked to repeated exposure to depigmenting or melanotoxic chemical agents. The number of such depigmenting chemical agents in commercial and industrial settings has rapidly increased over the past decades. In this review article, we aimed to raise awareness of chemical vitiligo by highlighting the most commonly implicated chemical agents and the characteristic diagnostic features of this skin condition.

Conflict of interest statement. None declared.

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