Vitiliginous Lesions Induced by Amyl Nitrite Exposure

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Chemical (or contact) leukoderma is a condition induced by local cutaneous exposure to chemicals or medicaments that are toxic to melanocytes and/or koebnerize preexisting vitiligo vulgaris. Chemicals known to induce leukoderma include phenol/catechol derivatives (eg, hydroquinone), sulfhydryls, contact sensitizing agents (eg, squaric acid dibutylester), and more recently imiquimod, among others. We report the case of a 37-year-old black man with human immunodeficiency virus who developed chemical leukoderma in the nasal and perioral areas within 4 weeks of spilling liquid amyl nitrite, which he had been inhaling as a recreational drug, on his lower face. The depigmented regions were treated with a biweekly regimen of 308-nm excimer laser treatment for a total of 78 sessions. More than 90% cutaneous repigmentation was achieved. Amyl nitrite–induced vitiliginous lesions are rare. We also discuss potential mechanisms of hypopigmentation from chemical agents and therapeutic options for chemical leukoderma.

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Chemical (or contact) leukoderma is the physical lightening or depigmentation of skin or hair following exposure to an exogenous chemical. The clinical appearance of chemical leukoderma may resemble a localized area of vitiligo but differs from contact/occupational vitiligo in that the depigmentation is confined to the area(s) of initial chemical exposure rather than spreading beyond the directly exposed skin.[1]

Many exogenous agents are used to lighten the skin and hair. The most commonly prescribed medications used to lighten or bleach the skin are hydroquinone and its derivatives (ie, monobenzyl ether, monomethyl ether, monoethyl ether).[2,3] Chemical leukoderma primarily has been described in vitiligo patients who use ammonia-based hair dyes, which have been found to be toxic to melanocytes, resulting in decreased or absent cutaneous pigmentation.[4] Other agents have been shown to induce leukoderma or vitiligo in patients following topical application, intralesional injection, or oral ingestion (Table).[5-9] Treatment of chemical leukoderma involves discontinued application of the offending agent(s) and use of topical vitiligo therapies. We report a case of facial chemical leukoderma following exposure to liquid amyl nitrite. The patient was successfully treated with an excimer laser.

Case Report

A 37-year-old black man with human immunodeficiency virus (CD4 lymphocyte count, 924 cells/mm^3; undetectable viral load) and seasonal allergies presented with acute-onset facial depigmentation of 3 months' duration. The patient did not have a history of vitiligo or other pigmentation disorders; he had no family history of vitiligo. He reported twice weekly recreational inhalation of amyl nitrite fumes for the last 3 to 4 years. Two months prior to presentation, the patient had accidentally spilled liquid amyl nitrite on the skin of the nasal and maxillary regions as well as the right nasolabial fold. Over 4 weeks the affected area began to peel, exposing "red, cracking skin" that was "sore, painful, itchy, and dry," according to the patient. Following localized facial skin peeling, the affected areas healed with depigmentation. The patient presented to the dermatology department seeking therapies for repigmentation.

Physical examination revealed well-demarcated depigmented patches along the distal nasal tip, nasal

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Mechanisms of Depigmentation for Known Select Compounds

Category	Specific Mechanism of Action	Topical Compound/Trauma	Other Pertinent Effects
Pre–melanin synthesis pathway	Decreased tyrosinase transcription	Tretinoin[5]	Unknown
	MITF downregulation	Lysophosphatidic acid[6]; C2 ceramides[7]; vitamin E[8]	Unknown
	Increased destruction of tyrosinase	Phospholipase D_2[9]; fatty acids[10]	Unknown
	Inhibition of tyrosinase maturation	Glycosphingolipids[11]	Unknown
Inhibition of melanin synthesis	Inhibition of tyrosinase via alternative substrate	Phenol/catechol derivatives (hydroquinone,[12] 4-hydroxyanisole,[13] monobenzone[14])	Oxidative stress–mediated melanocytotoxic effect
		4-S-cysteaminylphenol and 4-S-cysteinylphenol[15]	Melanocytotoxicity via alkylation of cell proteins
		Resveratrol[16]	ROS scavenger; COX-2 inhibitor; anticancer activity
		Aloesin[17]	Noncompetitive inhibition of tyrosine hydroxylase
		Azelaic acid[18]	Unknown
	Copper chelation (required for tyrosinase activity)	Kojic acid[19]; methyl gentisate[20]	Antioxidant activity; iron chelator; NF-κB inhibition
	Peroxidase inhibition	Ellagic acid[21]; ascorbic acid (vitamin C)[22]	Scavenger activity
		Glucocorticoids[22]	Unknown
Inhibition of melanosome transfer	Koebnerization of vitiligo due to irritant reaction or trauma	Serine protease inhibitors[23,24]; niacinamide (vitamin B_3)[25]; lectins[26]; neoglycoproteins[26]	Unknown
Melanocyte loss (vitiligo or complete chemical leukoderma)	Irritation/traumatic (koebnerization)	Tazarotene[27]; eyebrow plucking[28]; striae[29-31]; radiotherapy[32]; laser resurfacing[33]; scratching[34]	Unknown

Category	Specific Mechanism of Action	Topical Compound/Trauma	Other Pertinent Effects
Melanocyte loss (vitiligo or complete chemical leukoderma) (continued)	Autoimmune activation of TLR-7/TLR-8 pathway	Imiquimod[35,36]	Unknown
	Allergic contact dermatitis	Phenols/catechols[1,37] (paratertiary-amyl-phenol,[38] *p-tert*-butylphenol,[39] monomethyl/monobenzyl ether[40]); sulfhydryls[1]; cinnamic aldehyde[41]; alstroemeria[42]; squaric acid dibutylester[43]; carbyne[44]; cerium oxide[45]; diphencyprone[46]; nickel[47]; paraphenylenediamine[48]; primula[49]; arsenic[50]; chloroquine[51]; thiotepa[52]; physostigmine[53]; prolixin[54]	Unknown
Unknown		Imatinib[55-58]	Unknown

Abbreviations: MITF, microphthalmia-associated transcription factor; ROS, reactive oxygen species; COX-2, cyclooxygenase 2; NF-κB, nuclear factor κB; TLR, toll-like receptor.

alae, philtrum, and right nasolabial fold and maxilla following a splash pattern of amyl nitrite exposure (Figure, A and B). No nasopharyngeal mucosal lesions or ulcerations were present. No cervical lymphadenopathy was palpated. The patient was unwilling to undergo amyl nitrite patch testing or laboratory screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency.

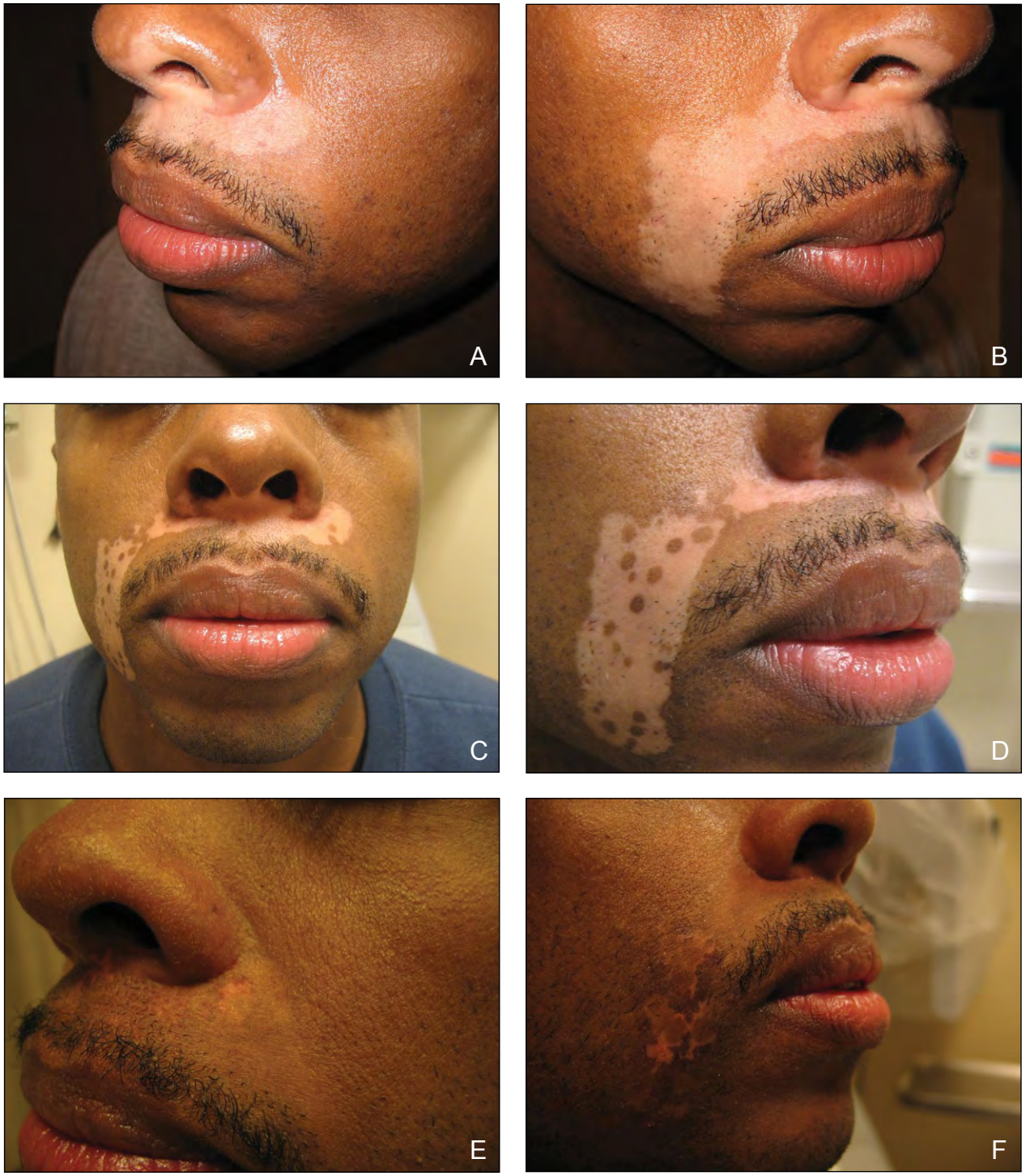
After topical treatments with tacrolimus ointment 0.1% and moisturizers were unsuccessful, a biweekly regimen of 308-nm excimer laser (XTRAC, PhotoMedex) treatments was started. The initial laser setting was 100 mJ/cm^2 with a treatment area of 100 cm^2; dose strength was increased by 10% to 15% per session until session 20, at which point a fixed dose of 320 mJ/cm^2 was administered at each subsequent session. The treatments were well tolerated by the patient. Evidence of perifollicular repigmentation was observed following the third treatment; with each successive treatment, repigmentation increased and the remaining areas of facial depigmentation decreased (Figure, C–F). Following roughly 42 treatment sessions, the depigmentation was almost completely resolved and the patient was satisfied with the cosmetic results. He continued the excimer laser therapy for a total of 78 sessions and achieved complete facial repigmentation.

Comment

Vitiligo is the loss of cutaneous pigment caused by reduced melanin production, inactivity of pigment cells, and/or melanocyte destruction. Pigmentary disorders can cause substantial psychological impairment in patients.[60]

Unlike vitiligo, chemical leukoderma is an acquired hypomelanosis caused by chemical exposure, especially to phenol derivatives and sulfhydryls, which inhibit or interfere with melanin biosynthesis and dispersal.[2] Several potential mechanisms of hypopigmentation for a number of chemical agents have been proposed (Table); based on our case, we add chemical destruction of melanocytes and koebnerization of vitiligo within areas of chemically damaged skin. The latter mechanism is the primary cause of complete leukoderma, as opposed to the partial leukoderma induced by topical hydroquinones in the absence of vitiligo.

Alkyl nitrites such as amyl nitrite ($CH_3[CH_2]_4ONO_2$), butyl nitrite, and isopropyl nitrite are illegal recreational drugs (referred to as "poppers" or



Depigmented patches involving the nasolabial folds, philtrum, columella, and nasal alae after exposure to liquid amyl nitrite (A and B). After 12 treatments with an excimer laser, follicular repigmentation was observed (C and D); notable repigmentation was observed after 42 treatment sessions (E and F).

"liquid gold")[61] whose vapors are inhaled intranasally or orally. Because of their vasodilatory and methemoglobin-inducing effects, these compounds often are abused for enhanced sexual arousal and relaxation of the sphincter muscles.[61] Common side effects associated with inhalation of alkyl nitrites include facial flushing, headache, dizziness, nausea, vomiting, decreased blood pressure, and an elevated pulse rate. Serious side effects including hypotension, tachycardia, syncope, and methemoglobinemia have been reported.[62,63]

Amyl nitrite–induced chemical leukoderma is rare. A possible mechanism of action is allergic contact dermatitis leading to melanocyte toxicity, similar to reactions caused by other known depigmenting contact allergens (Table). Cases of allergic contact dermatitis from alkyl nitrites have been reported in the literature.[64-66] Another potential mechanism of action is irritant contact dermatitis following exposure to liquid amyl nitrite, as koebnerization of vitiligo by irritants or physical trauma to the skin has been reported (Table). Additional possibilities include amyl nitrite–induced cytotoxicity of melanocytes as well as preexisting undiagnosed vitiligo that is either unmasked or exacerbated by amyl nitrite exposure.

The most likely mechanism of amyl nitrite–induced depigmentation is increased oxidative stress to the skin. Abuse of amyl nitrites can cause potentially fatal methemoglobinemia, especially in patients who are G6PD deficient.[67-78] Methemoglobinemia, a disorder in which increased levels of methemoglobin (an oxidized form of hemoglobin) cause tissue hypoxemia and increased oxidative stress,[79] is a mechanism strongly implicated in the pathogenesis of vitiligo.[80-96] Therefore, it is reasonable to hypothesize that cutaneous exposure to amyl nitrite may result in localized increases in oxidative stress from methemoglobinemia, resulting in melanocyte toxicity or death as well as the emergence of vitiligo in genetically susceptible individuals. Unfortunately, our patient declined G6PD testing.

Standard treatments of vitiliginous pigmentary disorders include topical preparations, photochemotherapy, surgical therapies, tattooing or cosmetic camouflage, and laser therapy. The 308-nm excimer laser has been found to be effective in the treatment of vitiligo[97]; efficacy in treating koebnerized vitiligo also has been demonstrated.[98] In our patient, treatment with an excimer laser was highly effective, and near-complete repigmentation of the affected area was achieved following roughly 42 treatment sessions.

Conclusion

We present a rare case of amyl nitrite–induced chemical leukoderma that was successfully treated with an excimer laser. The likely mechanisms of our patient's facial depigmentation include chemical melanocyte destruction through hypoxemia and increased oxidative stress as well as koebnerization of vitiligo within areas of chemically damaged skin. Amyl nitrite should be added to the list of agents that can potentially induce chemical leukoderma, and caution is advised for those individuals who may be exposed to this potentially depigmenting substance.

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