

# Diphenylcyclopropenone-Induced Vitiligo in a Patient with Alopecia Universalis

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## Key Words

Diphenylcyclopropenone · Vitiligo · Alopecia

## Abstract

Alopecia areata and vitiligo are autoimmune diseases, both associated with multiple autoimmune comorbidities. Many studies show colocalization of these diseases at the same anatomical site. Here, we have a case where both disorders were reported to present in the same patient. Diphenylcyclopropenone (diphencyprone, DCP) is used in the treatment of alopecia areata and may induce vitiligo in some patients. We report on one case of vitiligo that was induced by DCP during therapy for alopecia universalis. Alopecia areata and vitiligo share many susceptibility genes. Follicular melanocyte destruction may represent the link between the two diseases.

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## Introduction

Alopecia areata is a common skin disease that affects both children and adults, with 10% of patients presenting with more severe forms of the disease, i.e. alopecia totalis (AT) or alopecia universalis (AU). The lifetime risk of alopecia areata is estimated to be approximately 1.7%. Alopecia areata and its severe forms AT and AU are associated with other autoimmune diseases [1]. Vitiligo also affects both young and adult subjects and is associated with the autoimmune diseases thyroiditis, type I diabetes and alopecia areata. The worldwide prevalence of vitiligo ranges between 0.5 and 2% [2]. Alopecia and vitiligo share autoimmune etiology. Autoimmune diseases are characterized not only by multiple

autoimmune comorbidities, but in many instances also overlap and occur simultaneously in the same patient.

The coexistence of alopecia areata and vitiligo in the same patient was well documented more than a century ago [3]. For a patient with alopecia areata, the chance of getting vitiligo is double that of the normal population and is probably higher in patients with AT or AU, while the chance of a vitiligo patient getting alopecia areata is four times that of people without vitiligo. Colocalization of alopecia areata and vitiligo at the same anatomical site is a more complicated story and has been reported on in many studies. Many hypotheses have been suggested; however, it is actually a rare phenomenon [4–12].

During the treatment of patients with alopecia areata, the induction of vitiligo by contact sensitizers using diphenylcyclopropanone (diphencyprone, DCP) has been reported in many articles [13–19]. We report here on a case of DCP-induced vitiligo in a patient with AU.

### Case Report

A 52-year-old, diabetic, white male presented with an 18-year history of generalized hair loss. The patient was diagnosed as having AU. Upon examination, there was a universal loss of hair on the whole scalp, the face, the eyebrows and eyelashes, the arms, the axilla, the moustache and the beard areas. Dermoscopy did not show any cicatrization, but extensive areas of yellow dots and small areas with black dots and fine, small exclamation-mark hairs were noticed. There were no signs of regrowth in any of the affected areas. Nails and mucous membranes were normal. He had a positive family history of alopecia areata, but no family or personal history of vitiligo. Laboratory investigations showed an elevation of antithyroid peroxidase and antinuclear antibody (1:160) speckled pattern. Antiparietal cell antibody and anti-intrinsic-factor antibody were negative. Thyroid function test, homocysteine and vitamin B<sub>12</sub> showed normal levels. Before attending our OPD clinic, the patient underwent topical and intralesional steroid therapies at another hospital without improvement. In January 2011, we decided to initiate DCP therapy on the scalp only. Following the classic sensitization regimen, we started with one 2% application, followed by 0.0001% after 2 weeks, and then a weekly dose escalation guided by the appearance of erythema and the contact dermatitis reaction. The scalp showed erythema and crusts formation during therapy with no signs of hair regrowth. In July 2011, after 6 months of therapy and when we had reached a concentration of 0.01%, the patient presented with multiple white patches on the occipital and parietal areas of the scalp, diagnosed clinically and by Wood's light examination as vitiligo (fig. 1). We discontinued DCP and from July 2011 to April 2012, we administered a combined therapy of monochromic excimer laser radiation (308 nm; XTRAC, Photomedex, USA) in 3 sessions weekly (total dose 18.3 J/cm<sup>2</sup>) combined with topical pimecrolimus 1% cream twice daily. Depigmented areas showed a mild improvement, but this combined therapy had no effect on hair regrowth. The patient discontinued both lines of treatment. In September 2012, we started a low-pulse prednisone therapy, administering 80 mg prednisone per day on weekends (2 days of therapy and 5 days off treatment) for 4 months (until January 2013). In conjunction with prednisone, we prescribed topical prostaglandin E2 solution (Latisse: bimatoprost 0.03%) for the eyebrows and eyelashes. The hair regrowth was significant. After years, he at last achieved hair regrowth on his scalp, even though the vertex showed a moderate, androgenic, permanent loss of hair. His eyebrows recovered, but his eyelashes showed no response. He also experienced considerable though incomplete repigmentation of areas of skin with vitiligo. Oral pulse prednisone therapy was tapered and then discontinued after 4 months. Potent topical clobetasone

propionate 0.05% ointment was applied once daily to the scalp in addition to topical pimecrolimus 1% cream twice daily to the moustache and beard areas. Topical prostaglandin E2 solution was continued for the eyebrows and eyelashes. The topical therapies were continued for the next 16 weeks (until May 2013). The improvement was satisfactory for the patient, although tiny residual patches of colocalized alopecia and vitiligo can still be seen on the vertex and occipital areas (fig. 2). Regrowth of his facial hair is almost complete, especially his moustache. There has been no relapse and hair growth has continued. A maintenance therapy consisting of a topical weekend application of local agents is being continued with no intention of interruption. A spontaneous regression of both conditions cannot be ruled out.

## Discussion

Studies reporting anatomical colocalization of alopecia areata and vitiligo are displayed in table 1 [5–12]. The female-to-male ratio was 3:1. Age ranged from 9 to 60 years (mean 27.4 years). Fifty percent of the cases were Asian and were mainly from India. One 18-year-old girl was African-American and all other cases were Caucasian. In 1 case, alopecia preceded vitiligo while in another, the reverse happened and vitiligo preceded alopecia. In 2 cases, the two diseases presented simultaneously. Except for 1 case of AT, the alopecia in most reported cases was localized and was confined to limited anatomical sites, i.e. either the scalp or periorbital area (ratio 3:1). Pathological examination confirmed the diagnosis in 7 of 8 reported cases.

Studies describing DCP-induced vitiligo in patients with alopecia areata are displayed in table 2 [13–19]. The male-to-female ratio was 3:2. Age ranged from 12 to 67 years (mean 39.9 years). Race was equally distributed between Asians and Caucasians. Only severe forms of alopecia were reported, which necessitated the use of DCP. The duration of DCP-induced vitiligo varied from 6 weeks to 10.5 months. The DCP concentration varied from 0.0001 to 0.5%, although in most of the cases, depigmentation occurred with a relatively higher concentration of 0.5%. In 75% of the cases, vitiligo appeared as focal lesions on remote areas or areas adjacent to the DCP application site. Most DCP-induced vitiligo responds well to narrowband ultraviolet B (NB-UVB) therapy. Two studies in the 1990s reported pigmentary changes that were attributed to DCP application for alopecia areata, but the authors did not diagnose the depigmentation as vitiligo and so we decided to exclude these studies from table 2 [20, 21].

A genome-wide association study was performed on 1,054 alopecia areata cases and 3,278 controls; it revealed several susceptibility loci on eight genomic regions. Two regions out of eight shared 4 loci, and had a strong association with alopecia areata as well as being involved in generalized vitiligo. Three of the shared loci were within the human leukocyte antigen region 6p21.32 (HLA-DRA, BTNL2 and C6orf10) and one was in the region 10p15.1 (IL-2RA). These genes, except for C6orf10 (the function of which is unknown), influence the role of the immune system in the pathogenesis of both disorders as antigen presentation, costimulatory signaling and T cell proliferation [22].

Patients with autoimmune polyendocrinopathy candidiasis-ectodermal dysplasia/autoimmune polyendocrine syndrome type 1/polyglandular autoimmune syndrome type 1 present with a combination of Addison's disease, hypoparathyroidism, ectodermal dysplasia and/or chronic mucocutaneous candidiasis. They may also have alopecia areata and vitiligo, besides other multiorgan involvement such as gonadal failure, pernicious anemia, chronic active hepatitis, corneal dystrophy and enamel dystrophy [23].

Vogt-Koyanagi-Harada syndrome (VKH) is a well-known entity that may link alopecia areata and vitiligo. It is characterized by multisystem autoinflammation against melanocyte-containing tissues. It involves mainly the eyes, ears, meninges and skin. Skin features of VKH are vitiligo, poliosis and alopecia areata, which follow ocular and neurological symptoms. Incomplete forms of the disease may occur involving only one or more organs: the eyes, ears or skin. In many ethnic groups, VKH is associated with the susceptibility allele HLA-DRB1\*0405 that controls antigen presentation [24].

We would like to conclude that colocalization of vitiligo and alopecia areata is reported in many cases, and vitiligo is also reported to colocalize with other diseases like psoriasis and lichen planus [5]. DCP-induced vitiligo can occur in patients with alopecia areata as well as in patients with other skin diseases like verruca vulgaris [25]. The case presented in this study responded partially to phototherapy by excimer laser, but developed a higher degree of hair regrowth on a short course of pulse systemic steroid therapy. Areas with vitiligo were focal, localized and responded well to therapy. For both conditions, alopecia areata and vitiligo, spontaneous regression cannot be ruled out.

The mechanism of follicular melanocyte destruction in vitiligo and alopecia areata may provide a link between the two diseases. In the context of evolution and regression of alopecia areata, can we consider the appearance of white hairs to be a characteristic unique to vitiligo or is it a feature of the colocalization of vitiligo and alopecia areata?

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**Table 1.** Published reports on colocalization of alopecia areata and vitiligo in the same anatomical area

Author, year	Sex/ age	Country/ race	Duration/ sequence of vitiligo and alopecia	Site/ size	Investigations/ comorbidity	Therapy
Dhar and Kanwar [5], 1994	female/ 9 years	India/ Asian	1 year/ both at the same time	scalp, occipital area/ 2.5 cm	biopsy	N/A
Adams and Lucky [6], 1999	female/ 18 years	USA/ African- American	4 months/ N/A	scalp, occipital area/ 11 × 4 cm	biopsy, normal thyroid level	topical steroid
Cho and Lee [7], 2007	female/ 17 years	Korea/ Asian	1 year/ N/A	left eyebrow, eyelashes	biopsy, autoantibodies positive	N/A
Yadav et al. [8], 2009	female/ 12 years	India/ Asian	1 month/ N/A	left eyelid, eyelashes/ 15 × 4 mm	eye examination normal	prostaglandin E2 topical
Ramot et al. [9], 2010	female/ 60 years	Israel/ N/A	2 weeks/ N/A	scalp, vertex/ a few centimeters	biopsy, hypothyroidism, hypercholesterolemia	N/A
Rodriguez-Martin et al. [10], 2010	female/ 53 years	Spain/ Caucasian	2 years/ vitiligo preceded alopecia	whole scalp	biopsy, hyperthyroidism, anxiety disorder	N/A
Ozcan and Cevlik Aydoğan [11], 2012	male/ 8 years	Turkey/ Caucasian	1 month/ both at the same time	scalp, frontal area/ 4 × 2.5 cm	biopsy, blood sugar, thyroid function normal	N/A
Krishnaram et al. [12], 2013	male/ 42 years	India/ Asian	2 months/ alopecia preceded vitiligo	scalp, frontal area/ 11 × 6 and 4 × 3 cm	biopsy, CBC, chemistry and thyroid normal	topical steroid

**Table 2.** Studies published for DCP-induced vitiligo in patients with alopecia areata

Author, year	Sex/ age	Country/ race	Site/ size of alopecia	Induction duration/ DCP concentration	Site/ size of vitiligo	Therapy/ response
Hatzis et al. [13], 1988	1 male/28 years 2 females/19 and 53 years	Greece/ Caucasian	extensive alopecia	3–5 months/ 0.05–0.1%	treated area in 1 case: remote area	topical steroid/ only the male improved
Duhra and Foulds [14], 1990	male/37 years	UK/ N/A	AT	6 weeks/ 0.5%	tested area in forearm and adjacent area in nape and back	DCP-induced hair growth/ other vitiligo areas unchanged
Henderson and Ilchyshyn [15], 1995	male/23 years	UK/ Asian	AU	13 weeks/ 0.1%	treated and adjacent areas in face and neck	topical steroid/ only a weak response, self- improved
Pan et al. [16], 2009	1 male/67 years 3 females/12, 54 and 57 years	Singapore/ all Asians: 2 Chinese 1 Indian 1 Malay	extensive alopecia	10.5 months/ 0.0001–0.05%	in 2 of 4 cases: treated and remote areas	in 3 cases: NB-UVB, in 1 case: topical PUVA/ in 3 cases: a good response
Pires et al. [17], 2010	male/30 years	Brazil/ Caucasian	multiple patches on scalp, beard and eyelashes	5 months/ 0.02% on patch-test site: 30 days	treated and tested areas	topical steroid/ no response
Ganzetti et al. [18], 2010	male/34 years	Italy/ Caucasian	extensive alopecia	9 months/ 0.5%	treated and remote areas	NB-UVB/ a good response
Nilforoushzadeh et al. [19], 2012	1 male/37 years 1 female/42 years	Iran/ Caucasian	male: AT female: scattered areas	3–5 months/ 0.5%	remote areas	male: N/A female: vitiligo remained unchanged
Our study	male/52 years	Qatar/ Caucasian	AU	6 months/ 0.01%	treated areas, a few scattered patches	responded well to pulse steroid and to a lesser extent to excimer laser





**Fig. 1.** Photographs of the AU patient after the appearance of patches of vitiligo attributable to the application of DCP.



**Fig. 2.** Photographs of the patient after therapy; notice the regrowth of hair and repigmentation of vitiligo in most of the affected areas.