

ORIGINAL ARTICLE

Pigmented contact dermatitis due to therapeutic sensitizer as complication of contact immunotherapy in alopecia areata

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ABSTRACT

Pigmentary complication by contact immunotherapy (CI) for alopecia areata (AA) has been reported but its pathophysiology remains unknown. To characterize pigmentary complication by CI and its pathophysiology, we examined the incidence of hyperpigmentation in 186 consecutive patients treated with CI using diphenylcyclopropenone. From clinical data of AA totalis (AAT) or universalis (AAU) patients ($n = 78$), we studied the correlations between this complication and age, sex, atopic background, duration and treatment responsiveness, duration of CI, final concentration of diphenylcyclopropenone and administration of anti-histamines by χ^2 -test or Mann–Whitney U -test. Additionally, the histopathology of pigmentation was studied. As a result, 11 (5.91%) of the 186 patients had hyperpigmentation in this series. All of them had AAT or AAU, suggesting that the pigmentation is apt to occur in severe AA. When the AAT or AAU patients with ($n = 11$) and without hyperpigmentation ($n = 67$) were compared, those with pigmentation showed poorer responsiveness to CI ($P < 0.05$) but no significant tendency for other factors. Histopathologically, skin specimens showed lichenoid or vacuolar interface dermatitis with necrotic keratinocytes and dermal melanophages, consistent with pigmented contact dermatitis (PCD). Together, pigmentary complication by CI corresponds to PCD from therapeutic sensitizer, representing clinical indicator of poor responsiveness.

Key words: alopecia areata, diphenylcyclopropenone, histopathology, immunotherapy, pigmented contact dermatitis.

INTRODUCTION

Contact immunotherapy (CI) is widely performed for patients with alopecia areata (AA).¹ Its mechanism was recently reported to be mediated by Gr-1⁺ CD11b⁺ myeloid cells induced by chronic contact dermatitis using AA model mice.² Although in most cases the therapy is tolerable, in some instances side-effects can occur such as extensive eczematous reaction, facial edema, lymphadenopathy, contact urticaria, hyperpigmentation and hypopigmentation.³ Previously, the pigmentary complication by CI with diphenylcyclopropenone (DPCP) for AA was reported as “dyschromia in confetti”⁴ but its pathophysiology

still remained unknown. Here, we describe the hyperpigmentation caused by CI with DPCP and study its clinical and histopathological features.

METHODS

Patients

We surveyed patients with hyperpigmentation, characterized as persistent (≥ 3 months) or slate-colored lesions, on the scalp from 186 consecutive patients (66 men, 120 women) treated with CI using DPCP at Shin-Osaka Clinic for at least 3 months from January to June 2009. Their ages varied from 6–76 years and the median and mean age was 34.5 and 35.3 years,

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respectively. Because all of the patients were Asian, they had type III or IV skin. For sensitization to DPCP, we applied 1% DPCP in acetone on the patients' skin of the upper arms or scalp for 1 night using a Finn chamber mounted on Scanpor tape (Taisho Pharmaceutical, Tokyo, Japan). One week later, we confirmed erythematous reaction there. At 2 weeks after 1% DPCP application, we started CI with 0.0001% DPCP. The patients were treated by weekly or biweekly CI using DPCP solution in acetone. Until erythema, by which successful sensitization could be confirmed, appeared the concentration of DPCP was gradually increased as follows: 0.0001, 0.00025, 0.0005, 0.001, 0.0025, 0.005, 0.01, 0.025, 0.05, 0.1 and 0.2%. In addition, we administered the antihistamines⁵ fexofenadine hydrochloride ($n = 88$), olopatadine hydrochloride ($n = 5$), ebastine ($n = 4$), epinastine hydrochloride ($n = 2$), loratadine ($n = 2$), cetirizine hydrochloride ($n = 1$) and bepotastine besilate ($n = 1$). Skin biopsies were performed for the five patients with hyperpigmentation on the scalp after the informed consent was obtained from each patient.

Estimation of AA condition

The severity of AA was evaluated at the first visit using the SALT score proposed in the guidelines of the National Alopecia Areata Foundation^{6,7} as follows: S0, no hair loss; S1, 1–25% hair loss; S2, 26–50% hair loss; S3, 51–75% hair loss; S4, 76–99% hair loss; S5, AA totalis (AAT) and AA universalis (AAU). The regrowth score (RS) was estimated by decrease of SALT score (0–5), for example, regrowth from S3 to S1 was given as RS = 2 and exacerbation from S3 to S5 was given as RS = –2.⁵ To compare the

improvement in S1–4 (non-AAT/AAU) and S5 (AAT/AAU) patients, we defined the relative RS (RSS) as RS/initial SALT score, for example regrowth from S3 to S1 was given as RRS = 2/3 = 0.667.

Statistical analysis

To compare the data of S1–4 (non-AAT/AAU) ($n = 108$) and S5 (AAT/AAU) patients ($n = 78$) or S5 (AAT/AAU) patients with ($n = 11$) and without ($n = 67$) hyperpigmentation, the statistical difference of age, sex, atopic background (defined by complications or past history of atopic dermatitis, allergic rhinitis, bronchial asthma or positive radioallergosorbent test to *Dermatophagoides* antigen, house dusts or Japanese cedar pollinosis),⁵ AA duration, treatment responsiveness (RRS or RS, respectively), duration of CI, final concentration of DPCP and administration of antihistamines was evaluated by χ^2 -test for independence test or Mann–Whitney's *U*-test. $P < 0.05$ was considered statistically significant. For S5 (AAT/AAU) patients with and without hyperpigmentation, pruritus at the most recent point was estimated and compared by χ^2 -test for independence test.

RESULTS

Comparison of S1–4 (non-AAT/AAU) and S5 (AAT/AAU) patients

To compare the data of S1–4 (non-AAT/AAU) ($n = 108$) and S5 (AAT/AAU) patients ($n = 78$), the statistical difference of age, sex, atopic background, duration, RRS, duration of CI, final concentration of DPCP and administration of antihistamines was evaluated by χ^2 -test for independence test or

Table 1. Summary of clinical findings of S1–4 (non-AAT/AAU) and S5 (AAT/AAU) patients

	AA (S1–4)	AAT/AAU (S5)	Statistical analysis
No. of patients	108	78	
Age, mean (years)	37.9 $\pm$ 17.5	31.3 $\pm$ 13.4	$P = 0.0209^{**}$
Atopic background (+:–)	35:73	40:38	$P = 0.00961^*$
Sex (male : female)	38:70	28:50	NS*
Relative regrowth score	0.405 $\pm$ 0.340	0.231 $\pm$ 0.299	$P = 0.000380123^{**}$
AA duration, mean (months)	66.8 $\pm$ 64.6	110.0 $\pm$ 88.3	$P = 0.0000706^{**}$
CI duration, mean (months)	22.4 $\pm$ 20.2	23.8 $\pm$ 13.4	NS**
Final concentration of DPCP, mean (%)	0.022 $\pm$ 0.041	0.060 $\pm$ 0.078	$P = 0.00309^{**}$
Antihistamine administration (+:–)	52:56	55:23	$P = 0.00232^*$

Mean $\pm$ standard deviation, * χ^2 -test for independence test, **two-sided Mann–Whitney's *U* test. AA, alopecia areata; AAT, alopecia areata totalis; AAU, alopecia areata universalis; DPCP, diphenylcyclopropenone; NS, not significant; NT, not tested; S1–5, SALT score.

Mann–Whitney's *U*-test (Table 1). As a result, S5 (AAT/AAU) patients showed significantly ($P < 0.05$) lower age, higher incidence of atopic background, lower RRS, longer AA duration, higher final concentration of DPCP and higher frequency of antihistamine administration. The lower RRS and higher final concentration of DPCP in the S5 patients indicated that they showed poorer response to CI. Higher frequency of antihistamine administration for S5 AA was considered to be due to the higher association of atopic background, with which we had expected efficiency of antihistamines based on our previous observation.⁵ However, because in this study only patients treated with DPCP CI were studied, the difference of age and atopic background should be carefully interpreted and may not be true for the general AA population.

Correlation of clinical data and pigmentary complication

The diffuse slate-colored pigmentations macroscopically were seen on the scalp (Fig. 1a). Using dermoscopy, the reticular and granular pigmentations were observed, sparing the orifices and eccrine pores (Fig. 1b). Eleven patients suffered from persistent (≥ 3 months) or slate-colored lesion pigmentation on the treated scalp in this series, indicating its incidence as 5.91% (Table 2). All of them had AAT or AAU (S5) while average SALT score of the patients without pigmentation ($n = 175$) was 3.58 ± 1.31 , suggesting that the pigmentation is apt to occur in severe AA ($P < 0.05$, Mann–Whitney's *U*-test). For disease severity match, the patients having AAT or AAU (S5) with ($n = 11$) or without pigmentation ($n = 67$) were compared in terms of age, sex, atopic background, duration and treatment responsiveness, duration of CI and final concentration of DPCP. By χ^2 -test, sex, atopic background and administration of antihistamines did not significantly correlate with the pigmentary complication. While none of the patients with pigmentation showed any significant hair regrowth ($RS = 0$), the mean RS of the patients without pigmentation was 1.343 ± 1.533 , demonstrating poorer responsiveness to CI ($P < 0.05$, Mann–Whitney *U*-test), but there was no significant tendency about other factors such as age, AA duration, duration of CI and final concentration of DPCP (Table 3). To examine whether there

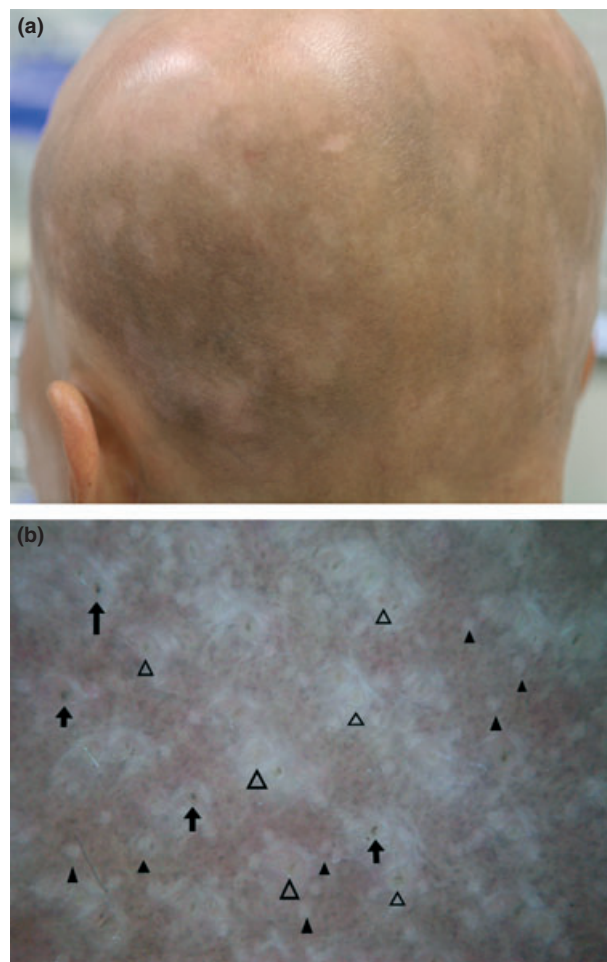


Figure 1. Clinical pictures of pigmentary complication in case 5 (Table 2). (a) Macroscopic appearance of pigmentary complication: diffuse slate-colored pigmentations were seen on the scalp treated with diphenylcyclopropenone. (b) Dermoscopic findings: the reticular and granular slate-colored pigmentations were seen on the scalp using dermoscopy. Cadaverized hairs are indicated by the arrows, yellow dots by the empty arrow heads, and eccrine pores, corresponding to the white dots, by the black arrow heads.

was significant difference of the extent of skin irritation between AAT/AAU patients with and without pigmentation, we checked the incidence of pruritus at the most recent point. Four of the 11 patients with pigmentation and 34 of the 67 patients without pigmentation felt pruritus. Therefore, this incidence did not differ between the two groups, indicating that the patients with pigmentation did not show significantly severe irritation. Although the patients were informed of a causal

Table 2. Summary of clinical and histopathological findings of the patients with pigmentary complication

No.	Clinical age/sex	Type of AA	Disease duration (month)	Duration of DPCP (month)	Final concentration (%)	Regrowth score	Atopy	Histopathological lichenoid	Vacuolar	Necrotic keratinocytes	Dermal melanophages
1	8/M	AAT	60	25	0.2	0	+	ND	ND	ND	ND
2	28/M	AAU	144	22	0.2	0	+	ND	ND	ND	ND
3	29/F	AAT	252	17	0.0005	0	+	ND	ND	ND	ND
4	31/M	AAU	180	18	0.2	0	+	ND	ND	ND	ND
5	32/M	AAU	28	21	0.1	0	+	+	+	+	+
6	35/F	AAT	156	60	0.2	0	–	–	–	–	+
7	36/M	AAT	216	36	0.2	0	–	–	–	+	+
8	37/F	AAU	192	5	0.0001	0	–	+	+	+	+
9	41/F	AAU	288	18	0.005	0	–	ND	ND	ND	ND
10	42/F	AAT	36	26	0.05	0	–	ND	ND	ND	ND
11	47/F	AAT	30	24	0.05	0	–	–	+	+	+

AT, alopecia areata totalis; AU, alopecia areata universalis; ND, not done.

Table 3. Correlation of clinical data and pigmentary complication

	AAT/AAU (S5)		
	Pigmentation (+)	Pigmentation (–)	Statistical analysis
No. of patients	11	67	
Age, mean (years)	33.3 ± 10.2	31.0 ± 13.8	NS**
Atopic background (+:–)	5:6	35:32	NS*
Sex (male : female)	5:6	23:44	NS*
Regrowth score	0 ± 0	1.34 ± 1.53	$P = 0.00348^{**}$
AA duration, mean (months)	143.8 ± 93.0	104.5 ± 86.9	NS**
CI duration, mean (months)	24.7 ± 13.9	23.6 ± 13.4	NS**
Final concentration of DPCP, mean (%)	0.110 ± 0.091	0.052 ± 0.073	NS**
Antihistamine administration (+:–)	6:5	49:18	NS*
Pruritus (+:–)	4:7	34:33	NS*

Mean ± standard deviation, * χ^2 -test for independence test, **two-sided Mann–Whitney's *U*-test. AAT, alopecia areata totalis; AAU, alopecia areata universalis CI, contact immunotherapy; DPCP, diphenylcyclopropanone; NS, not significant; S1–5, SALT score.

relationship between the treatment and hyperpigmentation, all of them were willing to continue CI as reported previously.⁴ We tried other treatments including topical corticosteroid for some patients and are now observing their effect.

Histopathological findings of pigmentary complication

Histopathology of skin biopsies from five patients with hyperpigmentation on the scalp was examined. The specimens showed interface dermatitis with lichenoid (2/5) or vacuolar alteration (3/5), necrotic keratinocytes (4/5) and dermal melanophages (5/5) (Fig. 2 and Table 1), consistent with pigmented contact dermatitis (PCD).^{8,9} Therefore, we suggest that pigmentary complication by CI for AA corresponds to PCD. In addition, we carefully observed hair follicle changes but there was no apparent interface reaction.

DISCUSSION

Previously, the pigmentary complication by CI with DPCP for AA was reported as “dyschromia in confetti” but its pathophysiology remained unknown.⁴ However, for the first time herein we showed that this hyperpigmentation is PCD from a therapeutic sensitizer, evidenced by the histopathological feature of interface dermatitis consistent with PCD. Its incidence (5.91%, 11/186 patients in this study) of our Asian patient series was higher than that reported previously in white subjects (1.65%, 4/243 patients),⁴ probably because of the dark complexion in Asians, agreeing with a previous description of higher incidence of PCD in Asians.¹⁰ Indeed, since the early 1980s, the prevalence of PCD from Naphthol AS has occurred.^{11,12} Also, during the outbreak of contact dermatitis by a whitener Tinopal CH3566, PCD

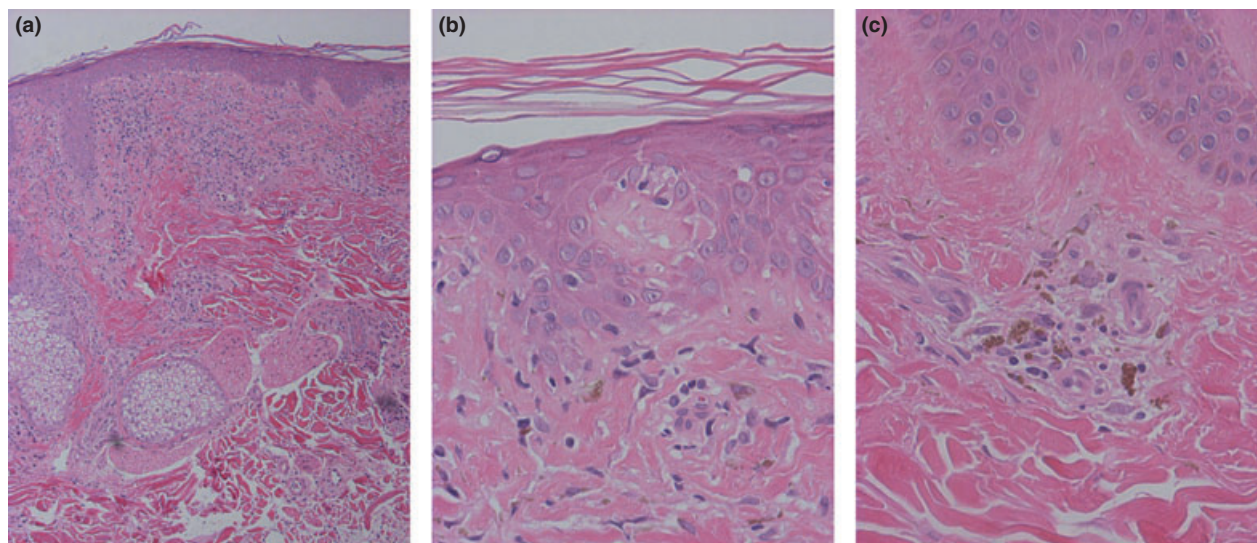


Figure 2. Histopathological findings of pigmentary complication. (a) Lichenoid infiltration of histiolympathocytic cells was seen beneath epidermis in case 5 (Table 2). (b) Necrosis of epidermal keratinocytes was seen in case 5 (Table 2). (c) Melanin deposition and melanophages were seen in the dermis of case 6 (Table 2).

occurred in white subjects with a dark complexion who all tanned very easily, and its incidence was 5.83% (7/120),⁸ which is similar to that of our case series here.

By comparison of the patients having AAT or AAU (S5) with ($n = 11$) or without pigmentation ($n = 67$) (Table 3), we suggest that the patients with hyperpigmentation are significantly refractory to the CI while the previous report did not point this out.⁴ One possible reason of this discordance is that in the previous report, if an adequate contact dermatitis by DPCP did not induce hair regrowth for 7 months, the treatment was ceased while such selection was not carried out in our cases. Further, this may be another reason for the lower incidence of pigmented complication through possibly choosing the patients with sufficient susceptibility to CI. Because the minimum induction concentration of DPCP after sensitization reportedly did not correlate with the patient age,¹³ the intensity of sensitization does not seem to be influenced by the age. Likewise, our data suggest no significant correlation between hyperpigmentation and age, indicating no predisposition for this complication. Likewise, we could not find any significant tendency of other factors such as atopic background, AA duration, duration of CI, final concentration of DPCP and administration of antihistamines. Finally, we found

that the pigmentary complication correlates positively with severity of AA and resistance to CI. Because AAT or AAU is basically recalcitrant, we do not believe that poorer responsiveness to CI shown here suggests absolute contraindication. To obtain eventual conclusion, further study is necessary by observing more patients for longer periods.

From our findings, dermal melanin deposition is caused by interface dermatitis, which obscures the dermis–epidermis junction. The mechanism of interface or lichenoid reaction of PCD is unknown. However, from the perspective of melanogenesis, phenylazonaphthol (PAN), a well-known contactant in PCD, reportedly induces a melanogenic-stimulating factor such as growth-related oncogene- α (GRO- α) using a PCD model of brownish guinea pig skins,¹⁴ suggesting that melanogenesis by the contactants, in part, causes the pathomechanism of PCD. Indeed, lentiginous eruption was reported to be induced during CI with squaric acid dibutylester (SADBE),¹⁵ suggesting that contact sensitizers such as DPCP and SADBE for CI may stimulate melanocyte activity. Alternatively, because melanocytes are possible targets as autoantigens in AA pathogenesis,^{16–18} it is of interest to elucidate relationship between auto-antigenicity of melanocytes and inhibitory effect of PCD on CI outcome.

Collectively, pigmentary complication by CI corresponds to PCD from therapeutic sensitizer, representing a clinical indicator of poor responsiveness.

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