Dermatology Practical & Conceptual

Antinuclear Antibody Positivity in Patients With Hair Loss After COVID-19 Infection

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Key words: SARS-CoV-19, hair loss, antinuclear antibody positivity, trichodynia

Citation: Manav V, Erdil D, Koku Aksu A. Antinuclear Antibody Positivity in Patients with Hair Loss after COVID-19 Infection. *Dermatol Pract Concept*. 2023;13(2):e2023081. DOI: https://doi.org/10.5826/dpc.1302a81

Accepted: August 29, 2022; **Published:** April 2023

Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Hair loss is one of the most common disorders after coronavirus disease 2019 (COVID-19) infection. This study aimed to investigate the relationship between COVID-19-related hair loss and antinuclear antibody (ANA) positivity and patterns.

Methods: ANA positivity and patterns were analyzed in 30 female COVID-19 patients with hair loss complaints and compared in terms of the presence of autoimmunity between patients with and without COVID-19 exhibiting hair loss.

Results: ANA positivity and cytoplasmic patterns were detected in 40% of the patients with COVID-19 infection and hair loss. Trichodynia and diffuse hair loss were observed in 63.3% and 53.3%, respectively.

Conclusions: In patients with COVID-19-related hair loss, diffuse hair loss and ANA positivity may be related to the high antibody levels triggered by COVID-19 infection.

Introduction

More than 175 million people were infected with coronavirus disease 2019 (COVID-19) within one year of the first COVID-19 infection reported in China in early December 2019 [1]. It has been reported that 80% of patients with COVID-19 infection develop one or more long-term symptoms. The most common symptoms are fatigue (58%), headache (44%), attention deficit (24%), and hair loss (25%) [2]. Skin findings have received increasing attention for the early

diagnosis of COVID-19. COVID-19-related skin findings include vascular eruptions, maculopapular eruptions (atypical forms of pityriasis rosea) [3], urticarial rash, vesicular, petechiae/purpuric eruptions, erythema multiforme–like rash, palmar erythema, perifollicular eruption, pruritus, mucosal rash, and androgenetic alopecia [4].

Autoimmune diseases that develop or worsen after COVID-19 infection have also been increasingly reported. These include connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus vasculitis, myositis, systemic sclerosis, and psoriatic arthritis) [5], multiple sclerosis, and autoimmune hepatitis [6] in adults, as well as rheumatic diseases [7,8] and type 1 diabetes in children [9].

Antinuclear antibody (ANA) tests were mainly developed for systemic lupus erythematosus screening. However, ANA positivity has also been detected in many rheumatic diseases and is an indicator of autoimmunity [10]. ANA positivity is not expected in non-scarring hair loss. In only one study, the rate of ANA positivity was reported in patients with pattern hair loss (30.4%) [11].

Objectives

Since COVID-19 can trigger autoimmunity, and as hair loss is one of the most common symptoms after COVID-19 infection, this study aimed to evaluate the relationship between the two and investigate the differences between autoimmunity- and non-autoimmunity-related hair loss.

Methods

This cross-sectional case-control study was performed between June and September 2021. The case group consisted of 30 patients who had contracted COVID-19 up to 12 weeks previously and had hair loss complaints. The control group consisted of 60 patients who complained about hair loss but did not have COVID-19. For the control group, each patient consisted of 2 consecutive patients who came to the dermatology outpatient clinic immediately after the patient selected for COVID-19- related hair loss.

Patients under the age of 18 years, patients with autoimmune or inflammatory diseases or acute or chronic infections, patients receiving any medications (corticosteroids, biological agents, antibiotics, or vitamin or mineral supplements), and pregnant or lactating women were excluded from the study. COVID-19 infection was confirmed using nasopharyngeal swabs and polymerase chain reaction tests.

Demographic characteristics (age and gender) and clinical findings (date of COVID-19 infection, duration of hair loss after COVID-19 infection (time from hair loss onset to presentation to the clinic), severity of hair loss, and presence of trichodynia, oily scalp, dandruff, and diffuse hair loss) were collected. Hair loss was recorded using the hair-shedding visual scale [12] as follows: < 50, 50–100, 100–150, and > 150 hairs/day. Additionally, a pull test was performed at four locations on the scalp. The pull test was considered positive when more than 10% of the hair at each location was removed after applying steady traction.

Chemiluminescence enzyme immunoassays were performed to measure vitamin B12 and ferritin levels using an Immunity 2000 device (Diagnostic Products Corporation). TSH (thyroid stimulating hormone) and anti-TPO (anti-thyroid peroxidase) levels were measured using an ARCHITECT ci16200 Integrated System (Abbot Diagnostics).

Antinuclear antibody titers and patterns were studied using enzyme-linked immunosorbent assays and immunofluorescence, with human epithelioma type 2 (HEp-2) cells used as the substrate. The ANA tests were first run at titers of 1:100 with both kits, and positive samples were reanalyzed with further serial dilutions (1:160, 1:320, 1:640, 1:1280, 1:2560, and 1:5120). C3 and C4 levels were measured using a Behring nephelometer and Beckman Reagent kits.

This study was approved by the tertiary hospital ethics committee (No. 2939; October 8, 2021). Written informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM). Histograms and the Kolmogorov–Smirnov test were used to assess data normality. In descriptive analyses, means ± standard deviations and medians were used. Categorical variables were compared using Pearson chi-squared test. The Mann–Whitney U test was used to evaluate non-normally distributed (nonparametric) variables between the case and control groups, and the Kruskal–Wallis test was used for comparisons between more than two variables. Spearman correlation coefficient was used to investigate correlations between variables. The ability of C3 and C4 values to predict ANA positivity was investigated using receiver operating characteristic (ROC) curves. Values of $P < 0.05$ were considered statistically significant.

Results

The mean ages of the patients in the case and control groups were 30.0 ± 11.2 and 29.2 ± 8.3 years, respectively. The difference was not statistically significant ($P = 0.952$). All patients were female.

There were no statistically significant differences in standard laboratory test values between the two groups (Table 1). Conversely, the duration of hair loss was significantly longer in the control group than in the case group ($P < 0.001$). In the case group, hair loss started 5.2 ± 3.4 weeks after COVID-19 infection.

Table 1. Comparison of standard laboratory test values of patients with covid-related hair loss and without covid-related hair loss.

	Covid-related hair loss group			Control			Total			
	Mean	SD	Medin	Mean	SD	Median	Mean	SD	Median	P[a]
Age (years)	30.03	±11.22	27.00	29.15	±8.32	27.00	29.44	±9.33	27.00	0.952
Duration of hair loss (weeks)	13.87	±7.54	12.00	20.50	±6.47	20.00	18.29	±7.49	20.00	**<0.001**
Vitamin B12(ng/L)	295.83	±125.18	280.50	300.13	±117.86	279.00	298.70	±119.66	279.50	0.911
Ferritin (µgr/L)	36.35	±28.63	32.60	33.33	±32.62	25.47	34.34	±31.22	26.38	0.419
C3(g/L)	1.27	±0.27	1.26	1.23	±0.30	1.26	1.24	±0.29	1.26	0.945
C4(g/L)	0.64	±2,20	0.25	0.29	±0.19	0.26	0.41	±1.28	0.25	0.566
TSH (mU/L)	2.65	±2.36	1.98	2.12	±0.97	2.04	2.30	±1.58	2.04	0.939

SD = standard deviation.
[a]Mann Whitney U Test

The rate of patients in the case group losing more than 100 hairs per day was 86%, whereas the corresponding rate in the control group was only 26% (P < 0.001). Trichodynia, oily scalp, and diffuse hair loss were significantly more common in the case group than in the control group (Table 2). Moreover, the case group had a significantly higher number of ANA-positive patients (40.0%) than the control group (11.6%) (P = 0.002). The rate of cytoplasmic ANA patterns in the case group was 83%, which was significantly higher than that in the control group (P = 0.001). In the control group, granular ANA patterns represented 71.4% of the patients. There was no significant relationship between ANA patterns and the severity of hair loss in the case group (Table 3).

The relationships between ANA positivity and clinical findings are shown in Table 4. In the covid-related hair loss group, the relationship between ANA positivity and trichodynia, duration of hair loss (week), oilyscalp, dandruff, diffuse loss of hair volume, pull test was investigated. Accordingly, in the covid-related hair loss group, all ANA positive patients had diffuse hair loss (12/12) whereas only %22 of ANA negative patients (4/18) had diffuse hair loss and pull test positivity were statistically significantly higher in patients with ANA positivity.In the case group, there were no significant relationships between ANA positivity and pattern or trichodynia (P = 0.279 and P = 0.670, respectively). Likewise, there was no significant correlation between hair loss duration and ANA positivity (r = –0.012, P = 0.949).

No significant relationships were observed between ANA positivity and C3 or C4 levels in the case group (P = 0.735 and P = 0.566, respectively). Furthermore, the ROC analysis indicated no significant cut-off values.

Conclusions

ANA positivity is detected in many viral and autoimmune diseases. However, studies on antibody responses after COVID-19 infection have not produced definitive results [13,14]. It remains unclear whether hair loss after COVID-19 infection is caused by the infection itself, the autoimmune response to the infection, or stress triggered by the COVID-19 pandemic. To our knowledge, the relationship between COVID-19-related ANA positivity and hair loss developing after the infection has not been previously investigated.

In this study, we detected ANA positivity in 40% of patients exhibiting hair loss after COVID-19 infection. This is consistent with previous studies reporting rates ranging from 21% to 64% [15-20]. Nevertheless, it is important to note that all COVID-19 patients in those studies had severe or moderate COVID-19, whereas the patients included in our study had mild COVID-19 and did not require hospitalization.

The rate of ANA positivity observed in this study is also in line with studies on hair diseases triggering stronger autoimmunity. Such studies have reported rates of 21.2% in telogen effluvium [21], 30.4% in pattern hair loss [11], and 46% in lichen planopilaris [22].

Surprisingly, in this study, cytoplasmic ANA patterns were observed in 83.3% of the patients with hair loss after COVID-19 infection. Trachtenberg et al., who reported 64% ANA positivity, found a highly dense and fine-speckled cytoplasmic pattern associated with COVID-19 worsening clinical severity scores [20]. However, as previously noted, all patients with hair loss in our study had mild COVID-19.

Chang et al detected cytoplasmic patterns at titers higher than 1:160 [23], whereas in this study, we observed

Table 2. Comparison of clinical examination and laboratory findings of patients with covid-related hair loss and without covid-related hair loss.

		Covid-related hair loss group N (%)	Control N (%)	Total N (%)	P[a]
Pre-exisiting TE	No	20 (66.67)	41 (68.33)	61 (67.78)	0.873
	Yes	10 (33.33)	19 (31.67)	29 (32.22)	
Amount of hair loss	50hairs/day	0 (0.00)	5 (8.33)	5 (5.56)	<0.001
	50-100hairs/day	4 (13.33)	39 (65.00)	43 (47.78)	
	100-150hairs/day	24 (80.00)	16 (26.67)	40 (44.44)	
	>150hairs/day	2 (6.67)	0 (0.00)	2 (2.22)	
Trichodynia	No	11 (36.67)	42 (70.00)	53 (58.89)	0.002
	Yes	19 (63.33)	18 (30.00)	37 (41.11)	
Oilyscalp	No	15 (50.00)	44 (73.33)	59 (65.56)	0.028
	Yes	15 (50.00)	16 (26.67)	31 (34.44)	
Dandruff	No	11 (36.67)	35 (58.33)	46 (51.11)	0.053
	Yes	19 (63.33)	25 (41.67)	44 (48.89)	
Diffuse loss of hair volume	No	14 (46.67)	45 (75.00)	59 (65.56)	0.008
	Yes	16 (53.33)	15 (25.00)	31 (34.44)	
Pull test	Negative	9 (30.00)	15 (25.00)	24 (26.67)	0.613
	Positive	21 (70.00)	45 (75.00)	66 (73.33)	
ANA positivity	Negative	18 (60.00)	53 (88.33)	71 (78.89)	0.002
	Positive	12 (40.00)	7 (11.67)	19 (21.11)	
ANA pattern	Cytoplasmic	10 (83.33)	0 (0.00)	10 (52.63)	0.001
	Granular	0 (0.00)	5 (71.43)	5 (26.32)	
	Nucleolar	1 (8.33)	0 (0.00)	1 (5.26)	
	Nuclear/Granular	1 (8.33)	2 (28.57)	3 (15.79)	
AntiTPO µL	<9	29 (96.67)	57 (95.00)	86 (95.56)	0.718
	>9	1 (3.33)	3 (5.00)	4 (4.44)	

ANA = antinuclear antibody; Anti-TPO = anti-thyroid peroxidase; TE = Telogen Effluvium
[a]Chi-Square Test

Table 3. The relationship between the antinuclear antibody pattern and the amount of hair loss in patients in the covid-related hair loss group.

		Amount of hair loss				
Covid- related hair loss group		50 hairs/day N (%)	50-100 hairs/day N (%)	100-150 hairs/day N (%)	> 150 hairs/day N (%)	P
ANA positivity	Negative	0(.00)	3(75.00)	14(58.33)	1(50.00)	0.784
	Positive	0(00)	1(25.00)	10(41.67)	1(50.00)	
ANA pattern	Cytoplasmic	0(00)	1(10.00)	9(90.00)	0(.00)	0.016
	Granular	0(00)	0(.00)	0(.00)	0(.00)	
	Nucleolar	0(00)	0(.00)	1(10.00)	0(.00)	
	Nuclear/Granular	0(00)	0(.00)	0(.00)	1(100.00)	

ANA = antinuclear antibody

Table 4. The relationship between antinuclear antibody positivity and clinical findings in patients in the covid-related hair loss group.

		ANA		
		Negative	Positive	
		N (%)	N (%)	P[a]
Trichodynia	No	8 (44.44)	3 (25.00)	0.279
	Yes	10 (55.56)	9 (75.00)	
Duration of hair loss (weeks), mean ± SD		12.89±6.48	15.33±9.00	0.520[b]
Oilyscalp	No	9 (50.00)	6 (50.00)	1.000
	Yes	9 (50.00)	6 (50.00)	
Dandruff	No	5 (27.78)	6 (50.00)	0.216
	Yes	13 (72.22)	6 (50.00)	
Diffuse loss of hair volume	No	14 (77.78)	0 (0.00)	<0.001
	Yes	4 (22.22)	12 (100.00)	
Pull test	Negative	8 (44.44)	1 (8.33)	0.034
	Positive	10 (55.56)	11 (91.67)	

[a] Chi-Square Test; [b]Mann Whitney U Test
ANA = antinuclear antibody.

cytoplasmic patterns even at a titer of 1:100. Furthermore, nucleolar patterns have been shown to be dominant in COVID-19 [15,17,18,23]. Thus, our results differ from those of previous studies in this respect. Massabki et al [24] and Eystathioy et al [25] suggested that cytoplasmic patterns at low and moderate titers had low clinical relevance. Conversely, Pazini et al reported that they were associated with autoimmune diseases even at low titers [26]. In our study, the cytoplasmic pattern of ANA was positive even at low titer, but it was also clinically significant.

Trichodynia is a symptom of local paresthesia often associated with telogen effluvium, androgenetic alopecia, and alopecia areata [27,28]. It is a crucial dermatological marker of the severity of hair disease and the response to treatment [29]. The pathophysiology of trichodynia is unclear, although substance P, a stress-related neuronal peptide, has been suggested to elicit the sensation [28]. According to previous studies, the rates of coexistence between telogen effluvium and trichodynia range from 34% to 73.6%, while the rates of coexistence between AGA (androgenetic alopecia) and trichodynia range from 26.4% to 36% [30-32]. Starace et al reported that telogen effluvium coexisted with trichodynia in 58.4% of COVID-19 patients [33], which is comparable to our findings.

Di Landro et al. suggested that severity of trichodynia might be directly related to the severity and intensity of hair loss [34]. In this study, diffuse hair loss after COVID infection was observed in 53.3% of the patients. The significant relationship between trichodynia and diffuse hair loss supports Di Landro et al.'s hypothesis. However, our results did not show a significant relationship between ANA positivity and trichodynia or between trichodynia and autoimmunity.

Since no financial support is received, ENA (extractable nuclear antigen) (anti-RNP, anti-Scl70, anti-Sm, anti-SS-A/Ro52, anti-SS-A/Ro60, or anti-SS-B/La), p-ANCA (perinuclear anti-neutrophil cytoplasmic antibodies), anticardiolipin IGM, and IGG, which are frequently measured in COVID-19 antibody studies, were not measured and were performed. scalp biopsies. Moreover, we did not evaluate patients stress levels using an anxiety scale to investigate the relationship between hair loss and stress.

In conclusion, hair loss after COVID-19 infection may be triggered by the release of autoantibodies in response to the infection. Cytoplasmic ANA patterns may be essential clinical markers for elucidating the pathogenesis of hair loss after COVID-19 infection.

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