

Original Article



Clinical Manifestation of Alopecia Areata After COVID-19 Infection or Vaccination

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ABSTRACT

Background: Alopecia areata (AA) is characterized by an autoimmune inflammatory response to hair follicles. Several studies have suggested that infection and vaccination can trigger an autoimmune process around hair follicles. Moreover, reports of AA and various other autoimmune diseases have increased since the coronavirus disease 2019 (COVID-19) pandemic became established.

Objective: We assessed the clinical characteristics and treatment response in patients who developed AA following COVID-19 infection or vaccination.

Methods: This retrospective study involved patients who had developed COVID-19 or received a COVID-19 vaccination within 3 months before the onset or aggravation of AA from January 2020 to December 2022.

Results: Fifty patients met the inclusion criteria. Eighteen patients had a history of COVID-19 infection, and 32 had a history of COVID-19 vaccination. The mean onset of AA after COVID-19 infection and vaccination was 5.22 ± 3.35 and 4.13 ± 2.73 weeks, respectively. The most common COVID-19-associated symptoms before AA were fever (88.9%) in the infection group and myalgia (50.0%) in the vaccination group. In the vaccination group, AA most commonly occurred after receiving the Pfizer-BioNTech vaccine (BNT162b2, 46.9%) or Moderna vaccine (mRNA-1273, 34.4%). The vaccination group showed more rapid improvement than the infection group; however, both showed significant improvement after 6 months of treatment of AA.

Conclusion: We examined the clinical characteristics and treatment responses of patients who developed AA after COVID-19 infection or vaccination. Further research is needed to evaluate the detailed pathogenesis and association between COVID-19 and AA.

Keywords: Alopecia areata; Autoimmune diseases; COVID-19; Infection; Vaccination

INTRODUCTION

Alopecia areata (AA) is an autoimmune inflammatory disorder that targets hair follicles, resulting in non-scarring hair loss. It shows no sex or racial disparities, and its cumulative lifetime incidence is approximately 2%. AA carries a considerable psychological impact, adversely affecting health-related quality of life^{1,2}.

Although the autoimmune pathogenesis of AA has been extensively researched, its triggers remain unclear. Potential triggering factors reportedly include emotional stress, metabolic or endocrine disorders, infections, drugs, and vaccines that may induce an interferon response, which plays a crucial role in the pathogenesis of AA¹⁻³.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

infection began spreading worldwide in December 2019 and was declared a pandemic in March 2020. Several types of vaccines have been developed and administered to prevent infection^{4,5}. Various autoimmune diseases, including AA, have been reported to develop after coronavirus disease 2019 (COVID-19) infection and vaccination. However, most of these publications have been case reports. The differences in clinical outcomes between patients who develop AA after infection versus vaccination remain unclear^{4,10}.

To fill this knowledge gap, we retrospectively collected and analyzed the clinical information of patients who developed AA after either COVID-19 infection or vaccination.

MATERIALS AND METHODS

Participants

Among 674 patients diagnosed with AA from January 1, 2020 to December 31, 2022, we enrolled 50 patients who had been diagnosed with AA by dermatologists and had a definite history of COVID-19 infection or vaccination within 3 months prior to the onset or aggravation of AA. The 3 types of AA among the patients were multiplex AA, alopecia totalis, and alopecia universalis. We categorized the 50 patients into a COVID-19 infection group and COVID-19 vaccination group (**Table 1**). Within these two groups, the patients were further classified into three subgroups according to their AA history: first episode, recurrence, and aggravation. Recurrence was defined as patients with newly developed AA who maintained the Severity of Alopecia Tool (SALT) score at 0% for the past year despite a history of AA. On the other hand, aggravation was defined as a pre-existing AA lesion before the onset of the COVID-19 event, with a worsening of the SALT score by >30% after the COVID-19 event. We excluded patients without photographs with which to define the SALT score or medical records of the SALT score at the time of the visit. We also excluded patients with underlying diseases that may be associated with hair loss and patients who had COVID-19-like symptoms without a confirmed diagnosis using a COVID-19 kit.

We recorded the patients' demographics and clinical characteristics, including sex, age at presentation, age at onset, COVID-19-associated symptoms, vaccination type, family history

of AA, presence of other comorbidities, AA subtype, SALT score, hair pull test result, duration of time from COVID-19 event to AA onset, and treatment methods.

Evaluation of treatment efficacy

We evaluated the treatment response at three time points: at the first visit, at 12 weeks, and at 24 weeks. To determine the degree of improvement in the AA lesions, we measured the SALT score at each visit and divided the patients into 5 groups according to their scores: S1 (0%–24%), S2 (25%–49%), S3 (50%–74%), S4 (75%–99%), and S5 (100%), as previously described¹¹.

Statistical analyses

All data were analyzed using GraphPad Prism 8.0.1 for Windows (GraphPad Software, San Diego, CA, USA). One-way analysis of variance and t-test were used to determine overall *p*-values reflecting trends between groups, and a *p* level of <0.05 was considered statistically significant.

Ethics approval

The study design was reviewed and approved by the Institutional Review Board of Chungnam National University Hospital (CNUH-IRB2022-05-023-003). We also gained approval from other participating institutes where necessary.

RESULTS

Demographics

We enrolled 50 patients who had been diagnosed with AA by dermatologists and had a definite history of COVID-19 infection or vaccination within 3 months before the onset or aggravation of AA (**Fig. 1**). The infection group comprised 18 patients with a mean age at onset of 29.89±17.57 years, and the vaccination group comprised 32 patients with a mean age at onset of 38.25±13.07 years. In both the infection and vaccination groups, most patients experienced their first episode of AA (55.6% and 84.4%, respectively). However, 38.9% of patients in the infection group developed aggravation of AA compared to only 3.1% in the vaccination group.

All patients in the infection group had more than one COVID-19-associated symptom, including fever (88.9%), respiratory symptoms (66.7%), myalgia (55.6%), and loss of taste or smell (16.7%). However, 43.8% of patients in the vaccination group had no vaccination-related symptoms. The mean SALT score before the COVID-19 event was 8.11%±19.39% in the infection group and 0.31%±1.77% in the vaccination group. After the COVID-19 event, the mean SALT score was 48.67%±33.16% in the infection group and 34.44%±29.59% in the vaccination group (**Table 2**).

Table 1. Patients diagnosed with AA during 2020–2022

Variables	Values
A total patients diagnosed as AA	674 (100.0)
COVID-19-associated AA	50 (7.4)
Infection	18 (2.7)
Vaccination	32 (4.7)

Values are presented as number of patients (%).

AA: alopecia areata, COVID-19: coronavirus disease 2019.

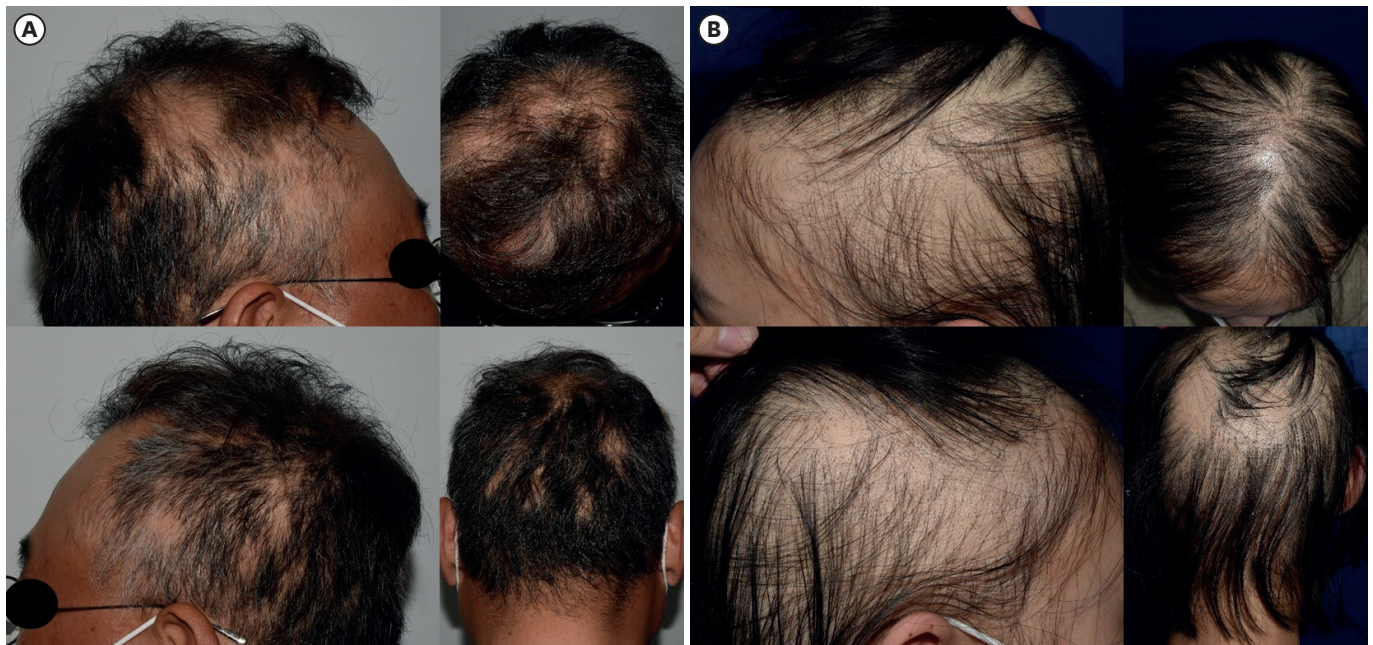


Fig. 1. Clinical pictures. (A) A 49-year-old male after 2 weeks of COVID-19 infection. (B) A 24-year-old female after 4 weeks of the second dose of Pfizer-BioNTech (BNT162b2) vaccination.

COVID-19: coronavirus disease 2019.

Table 2. Demographics and clinical characteristics of patients

Characteristics	COVID-19 infection	Vaccination
Total number of patients	18	32
Mean age at onset of AA (yr)	29.89±17.57	38.25±13.07
Sex		
Male	5 (27.8)	17 (53.1)
Female	13 (72.2)	15 (46.9)
Clinical subtype		
AA multiplex	11 (61.1)	21 (65.6)
Alopecia totalis	6 (33.3)	10 (31.3)
Alopecia universalis	1 (5.6)	1 (3.1)
Occurrence of AA		
1st episode	10 (55.6)	27 (84.4)
Recurrent	1 (5.6)	4 (12.6)
Aggravation	7 (38.9)	1 (3.1)
COVID-19 associated symptom		
Fever	16 (88.9)	8 (25.0)
Respiratory symptom	12 (66.7)	2 (6.3)
Loss of taste or smell	3 (16.7)	1 (3.1)
Myalgia	10 (55.6)	16 (50.0)
None	0 (0.0)	14 (43.8)
Mean SALT score (median)		
Before COVID-19 events	8.11±19.39 (0)	0.31±1.77 (0)
After COVID-19 events	48.67±33.16 (50)	34.44±29.59 (20)
Family history of AA	2 (11.1)	3 (9.4)
Autoimmune disease	0 (0.0)	0 (0.0)
Atopic disease	7 (38.9)	12 (37.5)
Atopic dermatitis	4 (22.2)	3 (9.4)
Allergic rhinitis	7 (38.9)	10 (31.3)
Asthma	1 (5.6)	0 (0.0)
Positive Anti-nuclear antibody	3 (16.7)	5 (15.6)
Positive hair pull test	12 (66.7)	17 (53.1)

Values are presented as mean ± standard deviation or number (%). COVID-19: coronavirus disease 2019, AA: alopecia areata, SALT: Severity of Alopecia Tool.

Table 3. Time between AA onset and COVID-19 infection and vaccination

Variables	1st episode	Recurrence	Aggravation	Total
Onset of AA after infection				
No. of patient	10	1	7	18
Mean time to occurrence after infection (wk)	4.90±2.92	4	5.86±4.26	5.22±3.35
Onset of AA after vaccination				
No. of patient	27	4	1	32
Mean time to occurrence after last vaccination (wk)	3.85±2.77	5.00±2.00	8	4.13±2.73

AA: alopecia areata, COVID-19: coronavirus disease 2019.

Time between COVID-19 infection/vaccination and AA onset

We next examined the temporal correlation between the COVID-19 event and AA onset (**Table 3**). The mean time to the development of AA after COVID-19 infection was 5.22±3.35 weeks, and this was not significantly different from the mean time in the vaccination group.

Association of COVID-19 vaccination type and dose with occurrence of AA

We analyzed the associations of the types and doses of COVID-19 vaccines with the occurrence of AA in the vaccination group. AA most commonly occurred after receiving the Pfizer-BioNTech vaccine (BNT162b2, 46.9%), followed by the Moderna (mRNA-1273, 34.4%), Janssen (Ad26.COVS.2.S, 9.4%), and AstraZeneca (ChAdOx1-S, 9.4%) vaccines. Additionally, the doses of the last vaccination before AA onset were evaluated. The rate of occurrence after the first and second vaccinations was the same at

Table 4. Treatment and change of SALT score in patients after 24 weeks

Variables	COVID-19 infection	Vaccination
SALT before treatment		
S1 (0–24)	5 (33.3)	13 (48.1)
S2 (25–49)	1 (6.7)	5 (18.5)
S3 (50–74)	4 (26.7)	4 (14.8)
S4 (75–99)	5 (33.3)	4 (14.8)
S5 (100)	0 (0.0)	1 (3.7)
SALT after treatment		
S1 (0–24)	10 (66.7)	21 (77.8)
S2 (25–49)	1 (6.7)	0 (0)
S3 (50–74)	1 (6.7)	1 (3.7)
S4 (75–99)	3 (20.0)	5 (18.5)
S5 (100)	0 (0.0)	0 (0.0)
Treatment method		
Intralesional steroids	3 (20.0)	13 (48.1)
Topical corticosteroids	13 (86.7)	27 (100)
Systemic steroids	5 (33.3)	13 (48.1)
Phototherapy	11 (73.3)	26 (96.3)
DPCP	2 (13.3)	1 (3.7)
Systemic immunosuppressant (e.g. cyclosporin, methotrexate)	11 (73.3)	19 (70.4)

Values are presented as number of patients (%).

SALT: Severity of Alopecia Tool, COVID-19: coronavirus disease 2019, DPCP: diphenylcyclopropenone.

40.6% each, and the rate of occurrence after the third vaccination was relatively low (18.8%).

Response to treatment

Among the 50 enrolled patients, we evaluated the treatment response in 42 patients for 24 weeks (**Table 4**). There was no statistically significant difference in the mean SALT score at baseline and after 24

weeks of treatment between the infection group and vaccination group (**Fig. 2A**). Interestingly, the patients in the infection group showed a slow response to treatment, with statistically significant improvement at 24 weeks of treatment ($p < 0.05$) (**Fig. 2B**). However, the patients in the vaccination group showed a more rapid treatment response after 12 weeks ($p < 0.01$) (**Fig. 2C**).

DISCUSSION

Various complications associated with COVID-19 have been reported since the COVID-19 pandemic became established. Many of these complications have been autoimmune diseases with skin manifestations, placing a significant psychosocial burden on patients^{4,12,13}. Several studies have proposed various hypotheses regarding the relationship between COVID-19 and autoimmune diseases^{14,17}. There are 2 representative hypotheses regarding the pathogenesis of AA after a COVID-19 event: a cytokine storm and molecular mimicry. A cytokine storm is a systemic inflammatory response triggered by a variety of factors, including infections and certain drugs¹⁴. Many studies have revealed that various cytokines, such as interferon- γ , play a crucial role in the pathogenesis of AA^{1,2}. Some authors have hypothesized that COVID-19 infection can trigger cytokine syndrome, based on laboratory data showing increased plasma levels of proinflammatory molecules in patients with COVID-19, and that the resultant cytokine storm triggers the development of AA¹⁵. Another hypothesis for the development of AA after COVID-19 is molecular mimicry^{16,17}. When COVID-19 infection occurs, antigen-presenting cells process the infectious

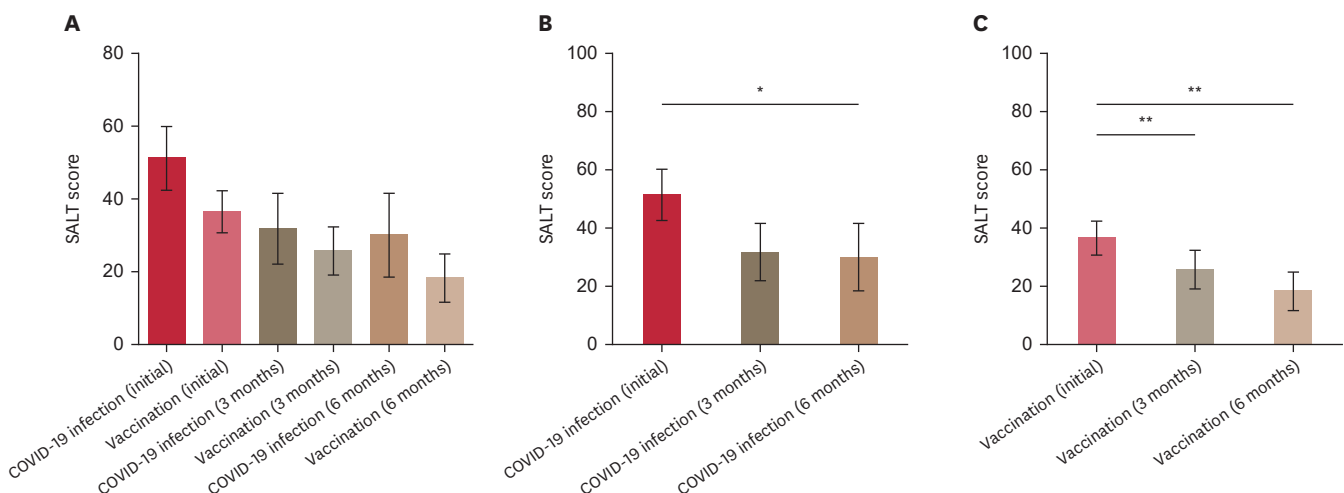


Fig. 2. Mean SALT score before and after treatment in COVID-19-associated AA patients. (A) There was a significant difference in the mean SALT score between the vaccination group at baseline, after 3 months, and 6 months of treatment. (B) In the infection group, no statistically significant difference in the SALT change after 3 months of treatment; however, there was an improvement in the SALT score after 6 months of treatment ($p < 0.05$). (C) In the vaccination group, there was a significant improvement in the SALT score both at 3 and 6 months of treatment ($p < 0.05$).

SALT: Severity of Alopecia Tool, COVID-19: coronavirus disease 2019.

* $p < 0.05$, ** $p < 0.01$.

agent into a pathogen peptide and present it to CD4+ T helper cells via major histocompatibility complex II. Autoreactive T cells are then generated as a result of the molecular mimicry between the pathogen peptide and the autoantigen. This ultimately causes cross-reactivity, which is the core of this hypothesis. Inflammatory cytokines produced by the autoreactive T cells lead to self-tissue destruction, i.e., they lead to the loss of immune privilege in hair follicles, resulting in tissue damage.

In this study, the mean onset of AA after COVID-19 infection and vaccination was 5.22 ± 3.35 and 4.13 ± 2.73 weeks, respectively. These onset times are shorter than those in previous studies^{9,10}. We assume that this difference is due to the time point at which AA occurred in each patient. However, only patients who developed AA within 3 months after the COVID-19 event were included. This strict criterion of 3 months may have been the cause of the shorter onset time compared to previous studies. Additionally, despite both groups showing a dramatic increase in SALT score after the COVID-19 event, the mean SALT score was higher in the infection group than in the vaccination group. This may have been due to the higher rate of aggravation in the infection group than in the vaccination group. As expected, the patients in the infection group showed more severe and numerous symptoms, with fever (88.9%) being the most common. In the vaccination group, myalgia (50.0%) was the most common symptom, and some patients had no symptoms. Moreover, there was no significant difference in the severity of AA between symptomatic and asymptomatic patients. Interestingly, the patients in the vaccination group showed more rapid improvement than those in the infection group. This difference may have been due to the higher initial SALT scores and active hair loss status in the infection group. When the type of COVID-19 vaccination that caused AA was monitored, Pfizer-BioNTech (BNT162b2) and the Moderna (mRNA-1273) vaccines showed a relatively high rate. This could be due to those vaccines being the most administered vaccines in South Korea during the pandemic, therefore additional research is needed to determine the difference in the risk of AA occurrence depending on the type of COVID-19 vaccine.

This was a retrospective study based on medical records and clinical photographs; therefore, many patients were excluded because of the difficulty in obtaining clinical information. For this reason, the number of patients included in this study was smaller than the number of patients with COVID-19-associated AA in actual clinical practice. This represents the main limitation of the present study. Additionally, it is deemed necessary to conduct systematic preclinical studies on the mechanism by which the COVID-19 virus induces or exacerbates AA.

Nevertheless, this study is clinically valuable because of the thorough evaluation of patients who developed AA in association with COVID-19 events, including infection and vaccination, with

assessment of the overall demographics and measurement of SALT scores and treatment outcomes at each visit. Because viral infection is a hypothesized trigger factor for AA, this study provides information that contributes to our understanding of the general characteristics of AA triggered by COVID-19 infection.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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