Chinese SLE Treatment and Research Group (CSTAR) Registry: prevalence and risk factors for chronic scarring alopecia in patients with systemic lupus erythematosus

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Abstract

**Background:** Scarring alopecia in systemic lupus erythematosus (SLE) patients caused reduced life quality and prolonged disease course. This case control study aims to survey the prevalence of scarring alopecia during the disease course of SLE and evaluate the risk factors for scarring alopecia in Chinese SLE patients.

**Methods:** SLE patients in Chinese SLE treatment and Research group (CSTAR) were recruited. Scarring alopecia was defined according to SLICC/ACR-DI which was collected during follow-up visits or via self-reported questionnaires. We collected demographic characteristics, common comorbidities, autoantibody profiles, disease activity status, major organ involvements and treatment strategies of these patients at registry. Univariate and multivariate logistic regression analyses were used to investigate the risk factors for scarring alopecia.

**Results:** We recruited 4792 SLE patients, and 374 (7.80%) patients had scarring alopecia. Mucocutaneous lesions (OR 2.062, p<0.001), high SLICC/ACR-DI (OR 1.409, p<0.001) and positive anti-Sm (OR 1.374, p=0.029) were risk factors for scarring alopecia, while renal (OR 0.714, p=0.028) and cardio-respiratory involvements (OR 0.347, p=0.044), and immunosuppressants treatment (OR 0.675, p<0.001) were significantly negative associated with it.

**Conclusions:** The prevalence of scarring alopecia in SLE patients is 7.80%. Active treatment strategies should be adopted to prevent scarring alopecia occurring.

**Background**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by high levels of autoantibody and multi-organ tissue damage [1]. Hair and scalp involvement is a common manifestation, presenting in more than half of the patients during the disease course [2-4]. Alopecia, its typical symptom, manifests with non-scarring or scarring. Non-scarring alopecia, more commonly, is defined in 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE as diffuse thinning or hair fragility with visible broken hairs [5, 6]. Regarding scarring alopecia, discoid lupus erythematous (DLE) runs a chronic course and ends up with distinctive pattern of scarring hair loss, which is included as one of skin damages in Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SLICC/ACR-DI) [7, 8].

Scarring alopecia predominantly affects 20-40 years old women, with median age 38 years old [9]. Once the scarring established, no treatment is effective to achieve hair regrowth [7]. This irreversible hair loss impacts the appearances of young SLE patients, causing considerable societal costs and reduced quality of life [10]. In addition, it is associated with prolonged disease course [9]. However, to the best of our knowledge, no study has learnt the scarring hair loss in SLE. This case control study aims to: 1) survey the prevalence of scarring alopecia during the disease course of SLE; 2) evaluate the risk factors for scarring alopecia.
Methods

Patients

Chinese SLE treatment and Research group (CSTAR) is the first multi-center Chinese SLE cohort with 104 participating rheumatology centers in 30 provinces in China. We recruited patients who were newly diagnosed SLE in CSTAR and fulfilled the 1997 SLE classification criteria revised by the American Rheumatology Association (ACR)[11] or 2012 SLICC classification criteria for SLE [6]. Patients were excluded if they had no follow-up data or some key baseline data were missing. This study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital, who is the leading site. All patients signed a written informed consent before recruitment.

Measures

Scarring alopecia was defined according to the SLICC/ACR-DI which was collected during follow-up visit or via self-reported questionnaires. It was a chronic irreversible alopecia presenting for at least 6 months (a typical figure shown in figure 1). Non-scarring alopecia was defined in 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE, which was diffuse thinning or hair fragility with visible broken hairs. We ruled out the patients who had already suffered from scarring alopecia in their registries.

Covariates were collected at registry, including demographic characteristics, autoimmune antibodies, disease activity and major organ involvements. Demographic characteristics included sex, age, body mass index (kg/m2) and comorbidities including smoking (defined as current or suspended in last 5 years), diabetes, hypertension and dyslipidemia (defined as Hypercholesterolaemia≥5.18 mmol/L and/or hypertriglyceridaemia≥1.69 mmol/h).

Autoimmune antibodies were evaluated in antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-Sjogren syndrome A (anti-SSA), anti-Sjogren syndrome B (anti-SSB), anti-ribosomal P protein (anti-rRNP), anti-ribonucleoprotein (anti-RNP), lupus anticoagulant (LA), anticardiolipin antibody (aCL), and anti-β2glycoprotein I (anti-β2GPI).

Disease activity was defined by the systemic lupus erythematosus disease activity index (SLEDAI). Disease damage was assessed by SLICC/ACR-DI (SLICC/ACR-DI excluded chronic scarring alopecia in risk factor analysis).

Major organ involvements included mucocutaneous lesions (acute, subacute and chronic lupus skin lesions), musculoskeletal involvement (arthritis and myoitis), serositis (pleuritis and pericarditis), renal disorders (24-h urine protein > 0.5 g/24 h or red blood cell casts in urine), neuropsychiatric disorders (as characterized by the ACR nomenclature and case definitions for the 19 neuropsychiatric lupus syndromes [12]), gastrointestinal tract involvement (peritonitis, lupus enteritis, malabsorption, Protein-losing enteropathy, pseudointestinal obstruction, hepatitis, acute cholecystitis and acute pancreatitis), cardio-respiratory (pulmonary arterial hypertension, myocarditis, arrhythmitis, valve dysfunction, pulmonary
hemorrhage/pulmonary vasculitis, indirect alveolititis/indirect pneumonia, shrinking lung syndrome, aortitis and coronaritis), and blood (hemolytic anemia, leukocytopenia, thrombocytopenia and thrombotic thrombocytopenic purpura).

Treatment strategies were collected when the patients ever used glucocorticoid, immunosuppressants (cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporine, and tacrolimus), hydroxychloroquine and biologic agents (TNFi, Rituximab, and Tocilizumab).

Statistical analysis

Categorical variables were expressed in numbers (%). Continuous variables were presented as mean (SD) or median (IQR). The normality was tested by the Shapiro-Wilk test. We performed univariate analysis on the independent variables to look for statistically significant factors. Factors with P-values of <0.10 were included in the multivariate analysis using logistic regression. SPSS (v. 23.0, SPSS Inc., IL, USA) was used for data analysis. Two-sided p-value less than 0.05 was considered to be statistically significant.

Results

Prevalence and baseline characteristics

A total of 4792 patients were recruited. Non-scarring alopecia was observed in 2283 patients (47.64%), while 374 patients (7.80%) suffered scarring alopecia. Among the 374 patients with scarring alopecia, 273 (72.99%) reported non-scarring alopecia at baseline. Table 1 depicted the demographic and clinical characteristics divided by scarring alopecia occurrence. Most patients with scarring alopecia were in their 30s, and 93.89% were female. 4.57% patients with scarring alopecia reported smoking, and 10.22% of them had hypertension.

Regarding disease activity and damage, for patients with scarring alopecia, SLEDAI was 7.06, and SLICC/ACR-DI was 0.59. 47.59% patients with scarring alopecia had anti-Sm antibody positive.

In patients with scarring alopecia, the most frequent forms of organ involvements were mucocutaneous (71.93%) and musculoskeletal system (58.29%), followed by haematological disorders (36.90%) and renal involvement (26.20%).

In terms of treatment strategies, 87.70% and 79.68% patients with scarring alopecia ever used glucocorticoid and hydroxychloroquine, respectively. Immunosuppressants were applied in 41.44% and 29.68% patients with and without scarring alopecia. Among patients with severe organ involvements (renal, neuropsychiatric, gastrointestinal tract and cardio-respiratory), 1029/1768 (58.20%) received immunosuppressants, while 913/3024 (30.19%) patients without severe organ involvements used these drugs (p<0.001).

Univariate analysis of risk factors for chronic scarring alopecia
Clinical variables between the two groups, “with scarring alopecia” and “without scarring alopecia”, were compared via univariate analysis. As shown in table 1, scarring alopecia was significantly associated with smoking (OR 1.689, P=0.048) and SLICC/ACR-DI (OR 1.241, P<0.001). Rates of anti-rRNP (OR 0.696, P=0.002) were lower in patients with scarring alopecia, while rates of anti-Sm (OR 1.403, P=0.002) were higher in alopecia group. The presence of mucocutaneous manifestations (OR 2.011, P<0.001) were positively related to scarring alopecia, renal (OR 0.678, P=0.001) and cardio-respiratory (OR 0.326, P=0.028) system involvements, however, were negatively associated with scarring alopecia. In terms of treatment strategies, immunosuppressants prevented the scarring alopecia occurring.

Multivariate analysis of risk factors for chronic scarring alopecia

We performed multivariate logistic regression analysis using variables that showed p<0.10 in univariate analysis. As shown in table 2, high SCLICC/ACR-DI, presence of anti-Sm and mucocutaneous involvement were risk factors for chronic scarring alopecia in SLE patients. Renal and cardio-respiratory involvements and immunosuppressants showed negatively association with scarring alopecia.

Since SLICC/ACR-DI was revealed to be a positive predictor for scarring alopecia, we further investigated the specific organ damages in patients with scarring alopecia. These patients had relatively high musculoskeletal damage (8.02%) and other skin damages (4.81%), including extensive scarring or panniculum other than scalp and pulp space, skin ulceration (excluding thrombosis) for >6 month.

Discussion

In the present study, we found the prevalence of chronic scarring alopecia in Chinese SLE patients was 7.8%. Mucocutaneous lesions, high SLICC/ACR-DI and positive anti-Sm were risk factors for scarring alopecia, while, renal and cardio-respiratory involvements, and immunosuppressants treatment were significant negative associated with it.

Hair loss is a frequent occurrence in SLE, divided as non-scarring and scarring alopecia. Discoid lupus erythematosus (DLE) is the typical clinical manifestation of chronic cutaneous lupus erythematosus, which is the only cutaneous lupus type healing with scarring [13]. In early stage, DLE lesions present inflammatory infiltration. However, patients with scalp DLE proceeds towards permanent and irreversible hair loss, once the replacement by fibrous tissue is established [14, 15]. The mechanism for the prevention of hair follicle regeneration and scarring occurring is still unknown. The localization of the hair follicle stem cells to the bulge area of hair follicle is one of explanation for this permanent hair loss process [14]. The inflammatory aggregation in where high concentration of antigen-presenting Langerhans cells associated with hair follicle stem cells leads to the destruction of the sebaceous gland, causing collagenous transformation [16].

DLE happened in 11.2% to 17.6% SLE patients [2], and scarring alopecia has been reported happening in 34% to 35% DLE patients [9, 17]. However, the prevalence of scarring alopecia in SLE is seldom studied. The present study included 4792 SLE patients and demonstrated the prevalence of scarring alopecia
7.80%, which is consistent with a cross-sectional study from Korea [5]. Although the prevalence for scarring alopecia is not that high, given its irreversible situation and reduced life quality of patients, we should learn the risk factors for scarring alopecia and try to prevent it from happening.

Smoking has been found an association with the prevalence or the activity of various autoimmune conditions [18]. Additionally, skin manifestation in SLE has been revealed to be related to tobacco use [19]. Moreover, smoking was found to worsen scalp DLE and make it resistant to treatment [20]. In the present study, we found smoking could be a potential risk factor for scarring alopecia. Smoking cessation should be emphasized for SLE management and scarring alopecia prevention.

Anti-Smith (anti-Sm) antibodies is a highly specific autoantibody in SLE, directly against seven Smith proteins that constitute the small nuclear ribonucleoprotein particles [21, 22]. Besides acting as a SLE classification criterion, anti-Sm antibody has been found to be related with specific subsets of system involvements [23] and disease activity [24]. In terms of skin manifestation, previous research revealed that anti-Sm antibody was associated with photosensitivity, malar rash and discoid rash [25, 26]. Also, SLE patients with DLE had significantly increased anti-Sm antibody positivity than patients without DLE [27], which is consistent with our study that anti-Sm antibody served as a significant risk factor for scarring alopecia. However, the mechanism behind this association needs further research.

In terms of organ involvements, we found that mucocutaneous lesion was predictors for scarring alopecia, while renal and cardio-respiratory involvements were negatively associated with it. Previous studies indicated that DLE among SLE patients was a marker for less severe disease, with a significantly higher rate for cutaneous manifestations [3] and infrequently occurring in lupus nephritis and other severe organ involvements [27-29]. This was in keeping with our result, which indicated possible different molecular pathways for scarring alopecia and other major organ involvements in SLE patients. In addition, the less frequent severe organ involvement suggested that when effective and strong treatment strategies were adopted to the patients with life-threatening organ involvements, these patients were less likely to develop scarring alopecia.

Immunosuppressive therapies are recommended for severe organ-threatening or life-threatening SLE [30]. Alopecia is a common side effect for immunosuppressive therapy, especially cyclophosphamide [31]. However, the present study revealed that immunosuppressants were negative associated with scarring alopecia. The possible explanations are as followed. First, as mentioned above, patients with major organ involvements had less possibility to present scarring alopecia, so the more usage of immunosuppressive therapies, in some extent, explained this negative association. Second, in spite of the alopecia side effect of these immunosuppressants, these drugs have powerful efficiency in controlling the SLE disease activity and protecting major organ from threatening damage. Additionally, the present study showed that renal and cardio-respiratory involvements, which are indicators for vital systemic involvements, were negatively related to scarring alopecia, indicating the efficacy of immunosuppressive therapy in maintaining low disease activity to prevent scarring alopecia occurring.
Higher SLICC/ACR-DI was demonstrated in our cohort of SLE patients with scarring alopecia. Since we excluded the chronic scarring alopecia factor when calculating SCLICC/ACR-DI in regression analyses, this high score could be attributed to the other skin damages except for scarring alopecia and comorbid musculoskeletal damage. It was demonstrated in previous study that DLE patients had more damage accrual, particularly scarring alopecia, skin scarring and skin ulcer [28], which explained the co-occurrences of scarring and other skin damages. In terms of musculoskeletal damage, high proportion of DLE patients were reported to have arthritis [29]. However, different results were found in other studies that DLE was associated with reduced risk of arthritis [27, 28] or no association between alopecia and arthritis [3]. In addition, muscle tenderness was revealed to be related with alopecia [3]. To the best of our knowledge, no consensus was made in the association of musculoskeletal damage and scarring alopecia. In the present study, our results suggested that skin and musculoskeletal damages in SLE patients may share the same molecular pathways, which needs further investigation.

Some limitations of the present study should be addressed. First, this is a preliminary and exploratory case control study, lacking the record of the exact scarring alopecia occurrence time point, and the self-report questionnaires could cause bias to the ascertainment of scarring alopecia. Second, to our knowledge, this is the only study to present the prevalence and risk factors for scarring alopecia in SLE patients, and was conducted only in Chinese SLE patients. The results should be verified in other SLE cohort population.

**Conclusions**

In summary, the prevalence of scarring alopecia in SLE patients is 7.80%. Positive anti-Sm antibody, mucocutaneous involvement and high SLICC/ACR-DI were risk factors for scarring alopecia, while renal and cardio-respiratory involvements and immunosuppressants usage were significantly negative associated. Active treatment strategies should be adopted to prevent scarring alopecia in SLE patients.

**Abbreviations**

SLE, systemic lupus erythematosus; CSTAR, Chinese SLE Treatment and Research Group; DLE, Discoid lupus erythematosus; SLEDAI, SLE disease activity index; SLICC/ACR-DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; ANA, Antinuclear antibody; anti-dsDNA, anti-double-stranded DNA; anti-Sm, anti-Smith; anti-SSA, anti-Sjogren syndrome A; anti-SSB, anti-Sjogren syndrome B; anti-rRNP, anti-ribosomal P protein; anti-RNP, anti-ribonucleoprotein; LA, lupus anticoagulant; aCL, anticardiolipin antibody; anti-β2GPI, anti-β2glycoprotein I

**Declarations**

**Ethics approval and consent to participate**
This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital. Informed consent was obtained.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

MTL, YRX and HL contributed to the conception and design of the study; YRX performed the data analysis and drafted the manuscript; MTL critically revised the manuscript; All authors contributed to the acquisition and interpretation of the data; MTL and XFZ are the guarantor and take responsibilities for the integrity of the work.

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**Tables**

**Table 1.** Demographic and clinical characteristics in patients with or without chronic scarring alopecia.
|                      | No scarring alopecia | Scarring alopecia (n=374) | OR (95%CI) | P value |
|----------------------|-----------------------|---------------------------|------------|---------|
| age                  | 33.51 (11.18)         | 33.06 (10.15)             | 0.996 (0.987~1.006) | 0.435   |
|                      | 4148 (93.89%)         | 344 (91.98%)              | 0.776      | 0.205   |
|                       |                       |                           | (0.524~1.149) |         |
| weight index (kg/m²) | 21.53 (3.07)          | 21.37 (2.88)              | 0.983 (0.946~1.022) | 0.382   |
|                      |                       |                           |            |         |
| liver and heart      |                       |                           |            |         |
|                       |                       |                           |            |         |
| CD4 count, mean±S.D. | 4.67 (5.95)           | 7.06 (8.26)               | -          | -       |
|                      |                       |                           |            |         |
| R-DI                 | 0.24 (0.61)           | 0.59 (1.05)               | 1.241      | 0.001** |
|                      |                       |                           | (1.090~1.414)c |         |
| test cases           |                       |                           |            |         |
| positive              | 4277 (96.81%)         | 354 (94.65%)              | -          | -       |
|                       | 3229 (73.09%)         | 277 (74.06%)              | 1.052      | 0.682   |
|                       |                       |                           | (0.827~1.338) |         |
| positive              | 1736 (39.39%)         | 178 (47.59%)              | 1.403      | 0.002** |
|                       |                       |                           | (1.135~1.734) |         |
| positive (n=3869)     | 2080 (57.89%)         | 175 (57.76%)              | 1.006      | 0.964   |
|                       |                       |                           | (0.793~1.275) |         |
| positive (n=3856)     | 740 (20.80%)          | 67 (22.41%)               | 0.910      | 0.513   |
|                       |                       |                           | (0.685~1.208) |         |
| rRNP positive         | 714 (22.19%)          | 75 (29.07%)               | 0.696      | 0.011*  |
|                       |                       |                           | (0.525~0.922) |         |
| positive (n=3797)     | 1386 (39.54%)         | 132 (45.21%)              | 0.793      | 0.058   |
|                       |                       |                           | (0.624~1.008) |         |
| Category            | Count (%)  | Reference Count (%) | OR (CI) | P-value |
|---------------------|------------|---------------------|---------|---------|
| Allergic             | 431 (18.48%) | 38 (22.09%)         | 0.799 (0.549~1.163) | 0.242   |
| Asthma               | 545 (17.77%) | 45 (17.79%)         | 0.999 (0.714~1.397) | 0.995   |
| (n=3086)            | 473 (16.53%) | 35 (15.56%)         | 1.075 (0.740~1.563) | 0.704   |
| Diabetes             | 2475 (56.02%) | 269 (71.93%)        | 2.011 (1.593~2.540) | <0.001*** |
| Gastrointestinal    | 2463 (55.75%) | 218 (58.29%)        | 1.109 (0.896~1.374) | 0.342   |
|                   | 463 (10.48%)  | 38 (10.16%)         | 0.966 (0.681~1.370) | 0.846   |
|                   | 1518 (34.36%) | 98 (26.20%)         | 0.678 (0.534~0.861) | 0.001**  |
| Gastrointestinal    | 78 (1.77%)   | 9 (2.41%)           | 1.372 (0.683~2.758) | 0.375   |
| Inflammatory bowel   | 48 (1.09%)   | 4 (1.07%)           | 0.984 (0.353~2.745) | 0.976   |
| Asthma               | 142 (3.21%)  | 4 (1.07%)           | 0.326 (0.120~0.884) | 0.028*  |
|                   | 1822 (41.24%) | 138 (36.90%)        | 0.833 (0.670~1.037) | 0.101   |
| Strategies (Ever)    |            |                     |         |         |
| Cytotoxic             | 3781 (85.58%) | 328 (87.70%)        | 1.201 (0.872~1.654) | 0.261   |
| Methylprednisolone    | 1831 (41.44%) | 111 (29.68%)        | 0.596 (0.474~0.750) | <0.001*** |
| Phenytoin             | 539 (12.20%) | 32 (8.56%)          | 0.673 (0.464~0.978) | 0.038*  |
| Mofetil               | 772 (17.47%) | 46 (12.30%)         | 0.649 (0.472~0.893) | 0.008**  |
| Neomycin              | 141 (3.19%)  | 9 (2.41%)           | 0.698 (0.352~1.383) | 0.303   |
| Neomycin              | 252 (5.70%)  | 17 (4.55%)          | 0.731 (0.352~1.383) | 0.223   |
|                | 324 (7.33%) | 17 (4.55%) | 0.588 | 0.038* |
|----------------|-------------|------------|-------|--------|
| **Lorozina**   |             |            |       |        |
| **3449 (78.07%)** | 298 (79.68%) | 1.102     | 0.469 |        |
| **Ents**       | 71 (1.61%)  | 4 (1.07%)  | 0.662 | 0.425  |

* p<0.05; ** p<0.01; *** p<0.001.

SLEDAI, SLE disease activity index; SLICC/ACR-DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; ANA, Antinuclear antibody; anti-dsDNA, anti-double-stranded DNA; anti-Sm, anti-Smith; anti-SSA, anti-Sjogren syndrome A; anti-SSB, anti-Sjogren syndrome B; anti-rRNP, anti-ribosomal P protein; anti-RNP, anti-ribonucleoprotein; LA, lupus anticoagulant; aCL, anticardiolipin antibody; anti-β2GPI, anti-β2glycoprotein I

Table 2 Multivariate analysis of risk factors associated with scarring alopecia

- **a**: Current or suspended in last 5 years
- **b**: Hypercholesterolaemia ≥5.18 mmol/L and/or hypertriglyceridaemia ≥1.69 mmol/L.
- **c**: SLICC/ACR-DI excluded chronic scarring alopecia in risk factor analysis.
- **d**: Immunosuppressants included cyclophosphamide, Mycophenolate Mofetil, azathioprine, cyclosporine, tacrolimus.
| Risk factors                              | OR (95%CI)            | P value   |
|------------------------------------------|-----------------------|-----------|
| Smoking                                  | 1.853 (0.985~3.488)   | 0.056     |
| SCLICC/ACR-DI (exclude chronic scarring alopecia) | 1.409 (1.207~1.646)   | <0.001*** |
| Anti-Sm                                  | 1.374 (1.034~1.825)   | 0.029*    |
| Anti-rRNP                                 | 0.808 (0.590~1.108)   | 0.186     |
| Anti-RNP                                 | 1.007 (0.744~1.362)   | 0.964     |
| Mucocutaneous                            | 2.062 (1.536~2.767)   | <0.001*** |
| Renal                                    | 0.714 (0.529~0.964)   | 0.028*    |
| Cardio-respiratory                       | 0.347 (0.123~0.970)   | 0.044*    |
| Glucocorticoid                           | 1.196 (0.800~1.789)   | 0.383     |
| **Immunosuppressants**<sup>a</sup>       | 0.675 (0.505~0.901)   | 0.008**   |

<sup>a</sup>: immunosuppressants included cyclophosphamide, Mycophenolate Mofetil, azathioprine, cyclosporine, tacrolimus.

SLICC/ACR-DI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; ANA, Antinuclear antibody; anti-Sm, anti-Smith; anti-rRNP, anti-ribosomal P protein; anti-RNP, anti-ribonucleoprotein;

*, p<0.05; **, p<0.01; ***, p<0.001.