Nonscarring alopecia in systemic lupus erythematosus: A cross-sectional study with trichoscopic, histopathologic, and immunopathologic analyses

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Background: Nonscarring alopecia in systemic lupus erythematosus (SLE) is widely recognized, but reports on its clinical, trichoscopic, histopathologic, and direct immunofluorescence (DIF) features are still limited.

Objective: To summarize the different clinical patterns, trichoscopic, histopathologic, and DIF features of nonscarring alopecia in SLE and to prove its association with disease activity.

Methods: Patients with SLE with and without nonscarring alopecia had full physical/trichoscopic examination and scalp biopsy. Their disease activity scores and laboratory data were evaluated and statistically analyzed.

Results: Thirty-two patients with SLE had different patterns of nonscarring alopecia, including mild diffuse alopecia (43.8% [n = 14]), severe diffuse alopecia (15.6% [n = 5]), patchy alopecia (28.1% [n = 9]), and lupus hair (12.5% [n = 4]). The most common trichoscopic findings were arborizing/interconnecting vessels (83% [n = 26]). Histopathologic examination showed interface changes along the dermoepidermal junction (87.5% [n = 28]) and follicular epithelium (40.6% [n = 13]). On DIF, homogeneous granular deposition was detected along the dermoepidermal junction (78.1% [n = 25]) and follicular epithelium (78.1% [n = 25]). When compared with 10 patients with SLE without alopecia, there was a significantly higher SLE Disease Activity Index 2000 score and prevalence of proteinuria (>1 g/d).

Limitations: This was a small, cross-sectional, single-center study.

Conclusions: Nonscarring alopecia in SLE shows lupus erythematosus–specific changes on histology and DIF. Hair loss in SLE can be considered as an indicator of active disease. (J Am Acad Dermatol 2019;81:1319-29.)

Key words: alopecia; dermoscopy; DIF; direct immunofluorescence; hair loss; histology; histopathology; LE; SLE; systemic lupus erythematosus; trichoscopy.

Hair loss is a common symptom of systemic lupus erythematosus (SLE), affecting 17.3%-85.2% of patients,[1-3] and its psychological impact can lead to a significantly lower quality of life.[4] Alopecia in SLE can be scarring, as in discoid lupus erythematosus (DLE), or nonscarring. Although the clinical, trichoscopic, histopathologic, and direct immunofluorescence (DIF) features of scarring alopecia have been well established, the definition of *nonscarring alopecia* is still unclear.

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The condition is often dismissed as telogen effluvium (TE), anagen effluvium, or alopecia areata (AA).

Previous studies have proposed different clinical patterns of nonscarring alopecia in SLE, including a diffuse type; a patchy type; and lupus hair, a condition with fragile hair along the anterior and peripheral hairlines. These entities have shown specific lupus erythematosus (LE) changes on histopathologic sections[1,3,5,6] and have recently been classified as LE-specific lesions, similar to acute, subacute, and chronic cutaneous LE.[7,8] However, reports of trichoscopic and histopathologic features of nonscarring alopecia in patients with SLE are sparse. In addition, past studies using objective assessment tools have shown conflicting results regarding an association between alopecia and SLE disease activity.[3,9]

This study aims to explore different clinical patterns of nonscarring alopecia, including its trichoscopic, histopathologic, and DIF features, as well as its association with SLE disease activity. To evaluate whether any detectable changes are responsible for clinical hair loss, we examined a comparison group of patients who had SLE but did not have any alopecia or scalp abnormalities.

CAPSULE SUMMARY

- Nonscarring alopecia in systemic lupus erythematosus comprises several clinical patterns, including diffuse, patchy, and lupus hair.
- The alopecia provides characteristic trichoscopic features and lupus erythematosus–specific changes on histopathologic/immunopathologic examinations and is associated with disease activity. The findings help elaborate the nonscarring alopecia criteria, leading to a more accurate diagnosis.

MATERIALS AND METHODS

This cross-sectional, analytic study was approved by the Mahidol University Institutional Review Board for Ethics in Human Research on July 13, 2017 (identification no. 06-60-09). A signed consent form was obtained from each patient before that patient was enrolled in the study. We recruited patients with SLE older than age 18 years from the dermatology and rheumatology outpatient clinics in Ramathibodi Hospital, Bangkok, Thailand. All of these patients fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria[10] and/or the American College of Rheumatology 1997 criteria.[11] Patients with nonscarring alopecia, defined as having diffuse hair thinning, single or multiple alopecic patches, or thinning of the anterior hairline, were included in the study. The exclusion criteria were patients with physical/trichoscopic examination results consistent with AA, androgenetic alopecia, trichotillomania, scarring alopecia, or any scalp dermatoses, as determined by a hair specialist. We also eliminated patients with any concomitant conditions that cause alopecia, such as hyperthyroidism, hypothyroidism, or iron deficiency; the presence of other connective tissue diseases; and/or recent (within 3 months) changes in medication.

After taking the history and physical/trichoscopic examination, we obtained 3 scalp biopsy specimens (vertical, horizontal, and DIF sections) from each patient. The biopsies were performed with a 4-mm punch biopsy instrument on the occipital area in patients with diffuse nonscarring alopecia and on the most severely involved areas in patients with localized alopecia. The vertical sections were stained with hematoxylin–eosin and assessed for pathologic changes from the epidermis down to the subcutaneous tissue (eg, interface changes, inflammatory infiltrate, morphology of follicles). Additionally, another specimen cut was stained with Alcian blue (pH 2.5) for mucin evaluation. The degree of mucin deposition was categorized as mild (sparse deposits), moderate (focal collection), or severe (significant deposits leading to separation of the collagen bundle).[12] The horizontal section was processed according to the description by Headington.[13] In addition to pathologic changes, detailed follicular counts and ratios were recorded. We did not discriminate between catagen and telogen follicles. Moreover, both vertical and horizontal sections were evaluated for CD123 immunohistochemistry. The last biopsy specimen for DIF was processed vertically and stained to detect the presence of bound immunoglobulins (IgG, IgM, IgA) and complement (C3). Furthermore, evaluations for other cutaneous and extracutaneous involvement and the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[14] were performed.

For further analysis, all of the mentioned parameters for this study group were compared with those of patients with SLE with normal hair density according to data from a previous normative study.[15] Informed consent for scalp/trichoscopic examination and biopsy was obtained from patients with SLE who fulfilled the SLICC or American College

Abbreviations used:

AA:	alopecia areata
DEJ:	dermoepidermal junction
DIF:	direct immunofluorescence
DLE:	discoid lupus erythematosus
IFN:	interferon
Ig:	immunoglobulin
LE:	lupus erythematosus
PDC:	plasmacytoid dendritic cell
SLE:	systemic lupus erythematosus
SLEDAI-2K:	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC:	Systemic Lupus International Collaborating Clinics
TE:	telogen effluvium

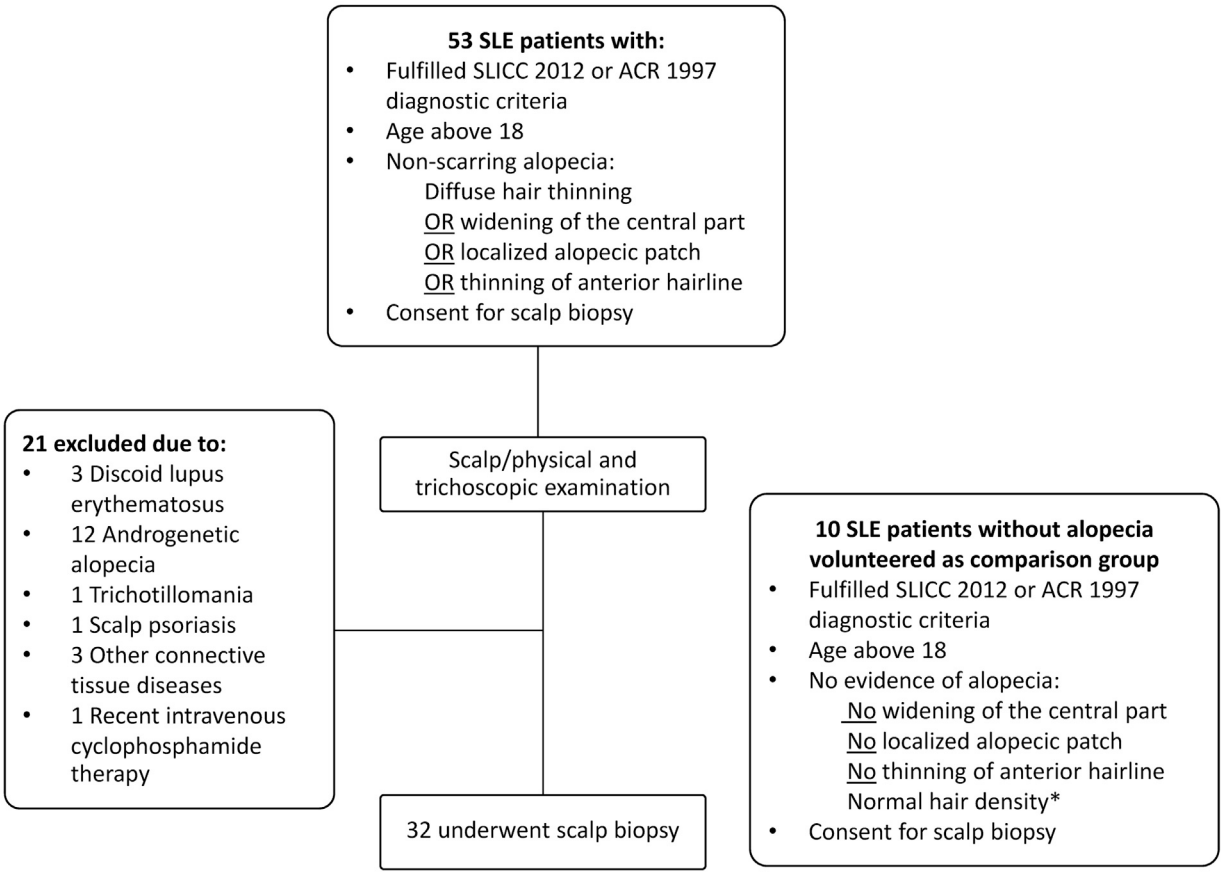
of Rheumatology diagnostic criteria but did not show evidence of alopecia. The biopsy was performed on the occipital area. In addition, data from different types of nonscarring alopecia were compared as a subgroup analysis. Results were statistically analyzed with Stata, version 14.0 (StataCorp LLC, College Station, TX), by using the chi-square test and Fisher exact test for categorical data and the *t* test, Mann-Whitney *U* test, and Kruskal-Wallis test for continuous data.

RESULTS

Fifty-three patients with SLE with nonscarring alopecia fulfilled the inclusion criteria. Of these, 21 patients were excluded, leaving 32 patients who had scalp biopsy. Ten patients with SLE without alopecia participated in the study as a comparison group and also had scalp biopsy. Of the 126 sections taken, 5 horizontal slides were excluded from the study due to inadequate tissue processing, leaving a total of 121 specimens from 42 patients. Details regarding study protocol are provided in Fig 1.

Patients with nonscarring alopecia

History and physical examination. Of 32 patients, 26 (81.3%) reported current ongoing hair loss. Various clinical presentations of nonscarring alopecia were observed. Fourteen patients (43.8%) had mild diffuse alopecia, and 5 patients (15.6%)



*Hair density was assessed by trichoscopic measurement. Normal hair density was defined as > 150 hairs/cm^2 according to previous normative study in Thai population.[15]
ACR, American College of Rheumatology; **SLE**, systemic lupus erythematosus; **SLICC**, Systemic Lupus International Collaborating Clinics.

Fig 1. Recruitment process and inclusion and exclusion criteria.

Table I. Baseline characteristics, trichoscopic, histopathologic, and direct immunofluorescence findings in patients with and without nonscarring alopecia

Characteristics and findings	Nonscarring alopecia group (n = 32)	Comparison group (n = 10)	*P* value
Baseline characteristics			
Age in years, mean (SD)	33.2 (11.1)	36.4 (9.7)	.42
Sex, n, M:F	4:28	0:10	.56
Duration of disease in years, median (range)	4.5 (0-25)	2.5 (1-19)	.55
Duration of alopecia in years, median (range)	2 (0-20)	—	—
Trichoscopic findings, n (%)			
Hair shafts			
Hair shaft thinning	24 (75)	3 (30)	.02*
Short regrowing hair	20 (62.5)	2 (20)	.03*
Hair shaft hypopigmentation	14 (43.8)	2 (20)	.27
Hair follicle openings/dots			
Black dots	6 (18.8)	0 (0)	.31
White dots	3 (9.4)	0 (0)	>.99
Follicular red dots	2 (6.3)	0 (0)	>.99
Perifollicular and interfollicular skin surface			
Blue-grey speckled pigmentation	8 (25)	0 (0)	.17
Brown honeycomb pigmentation	7 (21.9)	0 (0)	.17
Arborizing/interconnecting vessels	26 (81.3)	6 (60)	.21
Thick vessels	5 (15.6)	0 (0)	.32
Histopathologic findings			
Epidermal atrophy, n (%)	18 (56.2)	4 (40)	.48
Interface change, n (%)			
Along dermoepidermal junction	28 (87.5)	4 (40)	.006*
Along follicular epithelium	13 (40.6)	0	.018*
Lymphocytic inflammation, n (%)			
Superficial perivascular	24 (75)	5 (50)	.24
Superficial and deep perivascular	18 (56.3)	3 (30)	.15
Perifollicular	8 (25)	2 (20)	>.99
Peribulbar	7 (21.9)	3 (30)	.68
Perieccrine	4 (12.5)	0 (0)	.56
Presence of plasma cells, n (%)	10 (31.3)	1 (10)	.25
Reduction in size/number of sebaceous glands, n (%)	2 (6.3)	0 (0)	>.99
Mucin deposition, n (%)†			.007*
None	5 (15.6)	7 (0)	
Mild	16 (50)	3 (30)	
Moderate	5 (15.6)	0 (0)	
Severe	6 (18.8)	0 (0)	
Follicular counts and ratios			
Follicular unit, n, mean (SD)	7.6 (1.2)	8.3 (0.9)	.10
Follicular density, n, mean (SD)	17.6 (3.8)	23.7 (4.6)	.0004*
Anagen follicle, n, mean (SD)	14.5 (3.6)	21.8 (4.4)	<.001*
Catagen/telogen follicle, n, median (range)	3 (1-9)	2 (0-3)	.09
Percentage of catagen/telogen follicles, %, median (range)	16.7 (5.0-40.9)	9.1 (0.0-12.0)	.0029*
Terminal follicle, n, mean (SD)	14.8 (3.4)	21.9 (4.2)	<.001*
Vellus follicle, n, mean (SD)	2.8 (0.9)	1.8 (0.7)	.0031*
Terminal-to-vellus ratio, n, median (range)	5.7 (3.0-11.0)	11.5 (8.7-22.0)	<.001*
Fibrous streamer, n, median (range)	1 (0-4)	1 (0-2)	.98
Direct immunofluorescence findings, n (%)			
Homogeneous granular deposition			
Along dermoepidermal junction	25 (78.1)	4 (40)	.046*
IgG	10 (31.3)	2 (20)	.70
IgM	19 (59.4)	4 (40)	.47
IgA	4 (12.5)	3 (30)	.33
C3	12 (37.5)	1 (10)	.13

Continued

Table I. Cont'd

Characteristics and findings	Nonscarring alopecia group (n = 32)	Comparison group (n = 10)	*P* value
Along follicular epithelium	25 (78.1)	6 (60)	.41
IgG	20 (62.5)	6 (60)	>.99
IgM	18 (56.3)	4 (40)	.48
IgA	7 (21.9)	1 (10)	.66
C3	15 (46.9)	4 (40)	>.99
Epidermal nuclear staining	6 (18.8)	1 (10)	>.99
Colloid body	11 (34.4)	3 (30)	>.99
Perieccrine staining	6 (18.8)	3 (30)	.66
Perisebaceous staining	4 (12.5)	1 (10)	>.99

C, Complement; *F*, female; *Ig*, immunoglobulin; *M*, male; *SD*, standard deviation.
*Statistically significant.
†Alcian blue (pH 2.5) staining.

presented with severe diffuse alopecia involving more than 50% of their scalp hairs. Nine patients (28%) showed localized alopecic patches, and 4 (12.5%) had short fragile hair along the anterior hairline, resembling lupus hair in the literature.

Trichoscopic examination. Both scalp and hair shaft abnormalities were detected on trichoscopic examination. The most common features, observed in up to 81.3% of patients (n = 26), were abnormalities of the small blood vessels. These included numerous arborizing vessels located on interfollicular areas and interconnecting vessels that formed a plexus. In most patients, only the number of vessels increased, but in 5 patients (15.6%), the vessels were thick and tortuous, with diameters larger than the terminal hair shafts. The hair shafts in many patients were thin (75% [n = 24]) and hypopigmented (43.8% [n = 14]). Blue-grey speckled pigmentation was present in one fourth of the patients (25% [n = 8]). Other trichoscopic findings are listed in Table I.

Histopathology. Histopathologic examination showed some degree of interface changes (87.5% [n = 28]) along the dermoepidermal junction (DEJ), defined as having basal vacuolization and/or numerous melanophages below the epidermis. In 40.6% of patients (n = 13), basal vacuolar changes could be seen along the follicular epithelium. None had basement membrane thickening. Sparse lymphocytic infiltration was observed in superficial perivascular (75% [n = 24]), deep perivascular (56.3% [n = 18]), perifollicular (25% [n = 8]), peribulbar (21.9% [n = 7]), and perieccrine areas (12.5% [n = 4]). Horizontal sections showed an increase in the percentage of catagen/telogen (16.7%). The follicular architecture was well preserved, with regularly distributed follicular units in all sections. A reduction in the size and/or number of sebaceous glands was detected in 6.3% of patients (n = 2). Alcian blue (pH 2.5) staining showed mucin deposition in 84.4% of patients (n = 27). $CD123^+$ plasmacytoid dendritic cells (PDCs) were observed in the majority of patients with SLE with nonscarring alopecia (68% [n = 22]) and those without (60% [n = 6]). However, $CD123^+$ PDCs constituted less than 10% of the infiltration, and none showed the presence of clusters of 10 or more $CD123^+$ PDCs in patients with SLE either with or without alopecia.

Direct immunofluorescence. Homogeneous granular depositions of IgG, IgM, IgA, and/or C3 were apparent along the DEJ (IgG, 31.3% [n = 10]; IgM, 59.4% [n = 19]; IgA, 12.5% [n = 4]; C3, 37.5% [n = 15]) and/or extended down the hair follicles in 78% (n = 25) (IgG, 62.5% [n = 20]; IgM, 56.3% [n = 18]; IgA, 21.9% [n = 7]; C3 46.9% [n = 15]) of patients with nonscarring alopecia. Specimens from 6 patients with nonscarring alopecia (18.8%) showed epidermal nuclear staining. Moreover, perieccrine and perisebaceous staining could be seen in 31.3% (n = 10) (Table I).

Comparison between patients with SLE with and without alopecia

The age, sex, and duration of SLE were similar between the 2 groups. Despite having normal hair density, patients in the comparison group also exhibited some positive findings. Arborizing/interconnecting vessels could be observed on trichoscopy in 6 out of 10 patients (60%). Interface changes along the DEJ were evident on histopathologic and DIF examinations of 4 patients (40%). However, when compared with patients with nonscarring alopecia, patients with alopecia had a significantly lower prevalence of hair shaft thinning (P = .02) and short regrowing hair (P = .03) on trichoscopy. Biopsy specimens from patients with alopecia also showed significantly more interface

Table II. Baseline characteristics and trichoscopic, histopathologic, and direct immunofluorescence findings in patients with different subtypes of nonscarring alopecia

Characteristics and findings	Mild diffuse (n = 14)	Severe diffuse (n = 5)	Patchy (n = 9)	Lupus hair (n = 4)	*P* value
Baseline characteristics					
Age in years, mean (SD)	35.1 (10.4)	29 (14.3)	30.1 (10.6)	37.5 (12.0)	.60
Sex, n, M:F	1:13	0:5	2:7	1:3	.47
Duration of disease in years, median (range)	10 (0.2-25)	2 (0.1-15)	4 (0-14)	6.5 (2-23)	.24
Duration of alopecia in years, median (range)	4 (0-20)	1 (0.25-3)	2 (0-9)	2 (0.5-10)	.60
Trichoscopic findings, n (%)					
Hair shafts					
Hair shaft thinning	11 (78.6)	5 (100)	6 (66.7)	2 (50)	.34
Short regrowing hair	10 (71.4)	3 (60)	6 (66.7)	1 (25)	.45
Hair shaft hypopigmentation	4 (28.6)	3 (60)	5 (55.6)	2 (50)	.54
Hair follicle openings/dots					
Black dots	2 (14.3)	2 (40)	0 (0)	2 (50)	.07
White dots	1 (7.1)	0 (0)	2 (22.2)	0 (0)	.71
Follicular red dots	1 (7.1)	0 (0)	0 (0)	1 (25)	.42
Perifollicular and interfollicular skin surface					
Blue-grey speckled pigmentation	2 (14.3)	2 (40)	3 (33.3)	1 (25)	.58
Brown honeycomb pigmentation	2 (14.3)	3 (60)	2 (22.2)	0 (0)	.16
Arborizing/interconnecting vessels	12 (85.7)	5 (100)	7 (77.8)	2 (50)	.28
Thick vessels	2 (14.4)	0 (0)	3 (33.3)	0 (0)	.43
Histopathologic findings					
Epidermal atrophy, n (%)	8 (57.1)	2 (40)	4 (44.4)	4 (100)	.26
Interface changes, n (%)					
Along dermoepidermal junction	10 (71.4)	5 (100)	9 (100)	4 (100)	.21
Along follicular epithelium	3 (21.4)	2 (40)	6 (66.7)	2 (50)	.18
Lymphocytic inflammation, n (%)					
Superficial perivascular	11 (78.6)	3 (60)	6 (66.7)	4 (100)	.58
Superficial and deep perivascular	6 (42.9)	5 (100)	4 (44.4)	3 (75)	.13
Perifollicular	5 (35.7)	2 (40)	1 (11.1)	0 (0)	.31
Peribulbar	3 (21.4)	1 (20)	3 (33.3)	0 (0)	.82
Perieccrine	2 (14.3)	1 (20)	1 (11.1)	0 (0)	>.99
Presence of plasma cells, n (%)	5 (35.7)	2 (40)	1 (11.1)	2 (50)	.47
Reduction in size/number of sebaceous gland, n (%)	0 (0)	1 (20)	1 (11.1)	0 (0)	.35
Mucin deposition, n (%)[†]					.39
None	4 (28.6)	0 (0)	1 (11.1)	0 (0)	
Mild	5 (35.7)	3 (60)	5 (55.6)	3 (75)	
Moderate	2 (14.3)	0 (0)	3 (33.3)	0 (0)	
Severe	3 (21.4)	2 (40)	0 (0)	1 (25)	
Follicular counts and ratios					
Follicular unit, n, mean (SD)	8.5 (0.8)	6.5 (1.0)	7 (0.6)	6.8 (1.0)	.69
Follicular density, n, mean (SD)	20.5 (1.8)	13.8 (2.9)	15.4 (3.2)	16.0 (4.3)	.19
Anagen follicle, n, mean (SD)	17.6 (1.7)	11 (0.8)	12.1 (3.4)	12.0 (1.4)	.049*
Catagen/telogen follicle, n, median (range)	3 (1-6)	2 (1-6)	3 (1-5)	2.5 (2-9)	.80
Percentage of catagen/telogen follicles, %, median (range)	13.0 (5.0-27.3)	16.0 (8.3-33.3)	20.0 (5.6-35.7)	17.7 (14.3-40.9)	.11
Terminal follicle, n, mean (SD)	17.4 (1.6)	11.3 (1.9)	13 (2.8)	13 (4.2)	.11
Vellus follicle, n, mean (SD)	3.1 (0.8)	2.5 (1.3)	2.4 (1.0)	3 (0.8)	.66
Terminal-to-vellus ratio, n, median (range)	6.0 (1.5)	5.7 (3.6)	6.0 (2.2)	4.6 (1.8)	.22
Fibrous streamer, n, median (range)	0 (0-2)	1 (0-3)	1 (0-4)	1 (0-3)	.68
Direct immunofluorescence findings, n (%)					
Homogeneous granular deposition					
Along dermoepidermal junction	10 (71.4)	5 (100)	8 (88.9)	2 (50)	.29
IgG	4 (28.6)	2 (40)	4 (44.4)	0 (0)	.55
IgM	8 (57.1)	3 (60)	7 (77.8)	1 (25)	.40
IgA	1 (7.1)	1 (20)	2 (22.2)	0 (0)	.61
C3	4 (28.6)	3 (60)	4 (44.4)	1 (25)	.65

Continued

Table II. Cont'd

Characteristics and findings	Mild diffuse (n = 14)	Severe diffuse (n = 5)	Patchy (n = 9)	Lupus hair (n = 4)	*P* value
Along follicular epithelium	11 (78.6)	5 (100)	7 (77.8)	2 (50)	.39
IgG	8 (57.1)	4 (80)	7 (77.8)	1 (25)	.31
IgM	8 (57.8)	4 (80)	5 (55.6)	1 (25)	.54
IgA	2 (14.3)	2 (40)	3 (33.3)	0 (0)	.37
C3	8 (57.1)	3 (60)	3 (33.3)	1 (25)	.59
Epidermal nuclear staining	3 (21.4)	1 (20)	2 (22.2)	0 (0)	>.99
Colloid body	5 (35.7)	2 (40)	1 (11.1)	3 (75)	.17
Perieccrine staining	3 (21.4)	1 (20)	2 (22.2)	0 (0)	>.99
Perisebaceous staining	2 (14.3)	1 (20)	1 (11.1)	0 (0)	>.99

C, Complement; *F*, female; *Ig*, immunoglobulin; *M*, male; *SD*, standard deviation.
*Statistically significant.
†Alcian blue (pH 2.5) staining.

changes along the DEJ (P = .006) and follicular epithelium (P = .018) and mucin deposition (P = .007). Horizontal sections showed a significantly lower total hair count (P = .0004), terminal hair count (P < .001), anagen count (P < .001), and terminal-to-vellus hair ratio (P < .001) and a higher number of vellus hairs (P = .0031) and percentage of catagen/telogen hairs (P = .0029). On DIF, there was a significantly greater extent of homogeneous granular deposition along the DEJ (P = .046). All comparative results are summarized in Table I.

Comparison among subtypes of nonscarring alopecia in SLE

There were no differences found in baseline characteristics, trichoscopic, histopathologic, and DIF findings; serologic markers; extracutaneous manifestations; and SLEDAI-2K scores among patients with different subtypes of nonscarring alopecia, except for the anagen count, which was higher in patients with the mild diffuse type (P = .049) (Table II).

Association with disease activity

Various parameters were taken into account when assessing SLE disease activity (Table III). The SLEDAI-2K score used in this study, which integrates both laboratory assessments and systemic symptoms, is a validated assessment tool. The SLEDAI-2K was significantly higher in patients with alopecia when compared with patients without alopecia (P = .0001). However, when each component of the SLEDAI-2K was evaluated separately, there were no significant differences between the 2 groups. LE-associated laboratory markers collected at the time of scalp examination are also shown in Table III.

Renal involvement, defined by SLEDAI-2K as proteinuria exceeding 500 mg/d, was the most common extracutaneous feature, occurring in 40.6% and 20% of patients with and without nonscarring alopecia, respectively (P = .29). When we considered proteinuria at levels of 1 or 1.5 g/d, the cutoff points for other SLE severity assessment tools such as the SLE Index Score[16] and the British Isles Lupus Assessment Group disease activity index,[17] we found the results to be significantly higher in patients with nonscarring alopecia (P = .018 and .041, respectively).

As for other cutaneous manifestations, 2 out of 32 patients in the nonscarring alopecia group noted the recent onset of a photosensitive rash; 1 had a malar rash, and the other had erythematous papular lesions on the outer aspect of both forearms. No patients in the comparison group experienced any type of rash.

DISCUSSION

Nonscarring alopecia has long been accepted as a sign of SLE. The clinical entity, as mentioned in the SLICC diagnostic criteria, is "diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia."[10] Our study provides more details, such as the characteristics of hair loss and the trichoscopic findings (Tables I and II), which can be added to the SLICC criteria to enable more accurate diagnoses. Widely accepted SLE disease activity scores, such as the SLEDAI[14] and the British Isles Lupus Assessment Group index,[17] also assign points for nonscarring hair loss. Although widely recognized, this condition may deserve more attention. The true mechanism is still obscure, because nonscarring alopecia can be attributed to various dermatologic and systemic conditions that often coexist with SLE.

Our study has confirmed that nonscarring alopecia in SLE can have several clinical patterns, including diffuse, with varying degrees of severity;

Table III. Association between nonscarring alopecia and SLE disease activity

Characteristics and findings	Nonscarring alopecia group (n = 32)	Comparison group (n = 10)	*P* value
Characteristics			
ESR, mm/h, mean (SD)	39.2 (26.4)	40.2 (20.1)	.74
Low C3, n (%)	10 (34.5)	2 (28.6)	>.99
Low C4, n (%)	5 (22.7)	1 (12.5)	>.99
SLEDAI-2K score, median (range)	5 (2-25)	0 (0-8)	.0001*
Hematologic involvement			
Hemoglobin, g/dL, mean (SD)	11.58 (1.9)	11.63 (1.3)	.94
Hematocrit, %, mean (SD)	36.0 (5.4)	35.7 (4.6)	.87
White blood cells/mm^3, mean (SD)	5950 (2638)	6919 (3336.7)	.35
Platelets/mm^3, mean (SD)	288 156.3 (111 481)	254 800 (35 291.8)	.15
Renal involvement			
Creatinine, mg/dL, mean (SD)	1.6 (2.5)	0.68 (0.12)	.25
Proteinuria > 500 mg/d, n (%)	13 (40.6)	2 (20)	.29
Proteinuria > 1 g/d, n (%)	13 (40.6)	0	.018*
Proteinuria > 1.5 g/d, n (%)	11 (34.3)	0	.041*
Other extracutaneous involvement, n (%)			
Arthritis	4 (12.5)	0	.56
Neurologic involvement	1 (3)	1 (10)	.42
Serositis	1 (3)	1 (10)	.42

C, Complement; *ESR*, erythrocyte sedimentation rate; *SD*, standard deviation; *SLEDAI-2K*, Systemic Lupus Erythematosus Disease Activity Index 2000.
*Statistically significant.

patchy; or lupus hair. In concordance with a cross-sectional study of the prevalence of alopecia in SLE,[3] the diffuse type was found in the vast majority of patients. Patchy alopecia in SLE was also quite common, being observed in almost one third of our patients, and it was often the primary concern of young adult women. The presence of lupus hair was more subtle. In the 2 patients with lupus hair, the fragile appearance was not associated with alopecia. This finding is consistent with a previous report,[5] which stated that in chronically ill patients, lupus hair tends to persist long after the alopecia has resolved. In this study, there was no association between a particular subtype of nonscarring alopecia and a serologic marker or extracutaneous manifestation.

Trichoscopic examination suggested abnormalities beyond those of telogen or anagen effluvium. In the past, scalp trichoscopy in nonscarring alopecia in SLE has been reported, with interfollicular/perifollicular telangiectasias being the most common finding.[1,6,18] Similar to our study, the telangiectasias were described as arborizing, interconnecting, polymorphous, or tortuous. This interesting finding may be comparable to the tortuous capillaries with abnormal morphology in the nailfold.[19] Because scalp trichoscopic examination is simple and quick and dilated capillaries are readily visible, this technique may be applied during SLE diagnosis. Nevertheless, although telangiectasias are common in SLE, they are also detected on the scalp of patients with other autoimmune connective tissue diseases, including systemic sclerosis[20] and dermatomyositis.[21] A challenging concept would be to study the differences in scalp telangiectasia morphology between different autoimmune connective tissue diseases. The blue-grey speckled pattern is present only in patients with alopecia. Hypopigmentation of hair shafts is another common finding that must be differentiated from the effect of drugs. The antimalarial used in all of our patients was hydroxychloroquine. Hypopigmentation from chloroquine is well recognized, but for hydroxychloroquine, this adverse effect is far less common.[22]

Some histopathologic features may explain our trichoscopic findings. The blue-grey speckled pigmentation could result from melanin pigments and melanophages below the epidermis. The vessels on trichoscopy were expected to be seen on biopsy; however, superficial vessels appeared to be normative, without any dilatation or extravasated red blood cells.

In the past, the Gilliam classification of skin lesions associated with LE has regarded scarring alopecia as LE specific and nonscarring alopecia as LE nonspecific.[8] Our study results suggest otherwise, showing specific LE changes on scalp biopsy, that is,

epidermal atrophy, interface changes along the DEJ/follicular epithelium, and deposition of mucin, without signs of scarring (e.g., perifollicular fibroplasia, loss of follicular architecture, loss of sebaceous gland). These findings are consistent with results from recent studies and documentation of SLE scalp.[1,6,23] Because these findings were significantly more common in patients with alopecia, it is possible that SLE can directly insult the scalp and hair follicles. Aggregation of immune cells may induce basal vacuolization along the follicular epithelium, leading to progressive hair thinning and consequent hair loss.

When compared with those of patients with SLE without alopecia, the follicular counts of all types of nonscarring alopecia showed lower values of total hair, anagen hair, and terminal-to-vellus hair ratio, whereas the percentage of catagen/telogen hair was higher. Lichen planopilaris is a primary lymphocytic cicatricial alopecia that may have overlapping clinical and histopathologic features with nonscarring alopecia in SLE. Therefore, an increase in catagen/telogen hair found in our study may be a useful feature that differentiates nonscarring alopecia in SLE from lichen planopilaris, in which the catagen/telogen phase is significantly decreased or absent.[24] An increase in the percentage of catagen/telogen hair and a decrease in the terminal-to-vellus hair ratio can also be observed in AA and androgenetic alopecia.[25,26] Care should be taken to distinguish AA from patchy nonscarring alopecia in SLE to avoid overdiagnosis of AA. However, other histopathologic characteristics, as well as the follicular count values provided in this study, may help differentiate nonscarring alopecia in SLE from both conditions.

There have been speculations that nonscarring alopecia in SLE more likely fits the early stage of DLE, rather than being a separate condition, because its initial clinical presentations and histopathologic features may be similar.[27] The patchy type may further raise suspicion. However, unlike DLE, nonscarring alopecia in SLE occurs in cases of active SLE and has been reported to subside once the systemic disease is under control.[1,6] Moreover, we found no histopathologic differences among subtypes of nonscarring alopecia in SLE, which may indicate that they share a similar pathomechanism affecting the hair and scalp. Although early DLE cannot be entirely excluded, we believe that the alopecia in our patients was compatible with nonscarring alopecia in SLE rather than early DLE.

There is currently well-established evidence that PDCs and their production of type I interferons (IFNs) play a critical pathogenic role in cutaneous lupus erythematosus and SLE.[28] PDCs are demonstrable immunohistochemically by their surface expression of the interleukin 3 receptor-α chain (CD123). The presence of $CD123^+$ PDCs in significant numbers and their patterns of distribution (clusters/aggregates) holds a diagnostic value in cutaneous LE.[29] Our findings showed that $CD123^+$ PDCs constituted a small proportion of the infiltrate in patients with SLE both with and without alopecia, and no patients showed the presence of clusters of $CD123^+$ PDCs. This may be due to the presence of merely sparse inflammation in our biopsy specimens. On the basis of this result, we believe that CD123 immunohistochemical staining may not be useful for differentiating nonscarring alopecia in SLE from other types of nonscarring alopecia.

The involvement of follicles was also evident on DIF as homogeneous granular deposition along the follicular epithelium, although the differences between groups did not reach a significant level, possibly because of the small number of participants and the fact that DIF does not reflect real-time changes but displays any past insult on the follicles. Similar processes may have been observed in other autoimmune connective diseases. In a histopathologic study of dermatomyositis scalp, also presenting with nonscarring alopecia, biopsy samples showed epidermal atrophy, telangiectasia, mucin, and interface dermatitis.[12]

The mechanism of nonscarring alopecia in SLE remains to be discovered. Cutaneous LE results from a combination of genetic predisposition, ultraviolet radiation, recruitment of T cells, and a plethora of chemokines and cytokines.[30] Involvement of hair follicles may share a similar pathophysiology, further complicated by the dynamic nature of the hair cycle. We speculate that a high level of proinflammatory cytokines and an aggregation of immune cells during SLE exacerbations may negatively affect the hair growth cycle. Type I IFNs play an important proinflammatory role in both cutaneous lupus erythematosus and SLE.[31] Although the inhibition of the anagen phase and premature hair shedding are primarily linked to IFN-γ,[32] increasing evidence suggests that IFN-α may also have a similar effect on hair follicles.[33,34] Reduction of follicular density in the absence of other scarring signs on histopathology may show a biphasic pattern of alopecia in SLE in which the early process has no scarring, but follicular dropouts become apparent later.[23] Persistently active SLE may impair the follicular stem cell functions, leading to exhaustion of their proliferative capacity and subsequent permanent follicular degeneration.

Regarding disease activity, nonscarring alopecia is associated with significantly higher SLEDAI-2K scores. With renal involvement, the association was evident only in patients with proteinuria above 1 g/d. The high proteinuria level reflects a severe and higher class of lupus nephritis and suggests that the connection between nonscarring alopecia and renal involvement is limited to severe disease. A large prospective cohort is required to verify these findings.

The limitations of our study include its cross-sectional, single-center nature, which allowed no follow-up period and restricted the study population to Southeast Asians. In addition, the main differential diagnosis of diffuse nonscarring alopecia is TE. In this study, we have attempted to eliminate TE by excluding all other triggers. Moreover, our trichoscopic, histopathologic, and DIF results indicated an autoimmune process on the scalp. Nevertheless, TE could not be excluded entirely because active SLE inevitably puts the body under physical stress. The combination of both TE and nonscarring alopecia in SLE may coexist in some patients. Caution should also be applied with patchy nonscarring alopecia in SLE and AA. Ye et al[6] reported significant trichoscopic and histopathologic differences between the 2 conditions. Moreover, differentiating patchy nonscarring alopecia in SLE from early DLE may be difficult and rely on their characteristic trichoscopic and histopathologic findings. In practice, it is crucial for clinicians to consider all 3 conditions in a patient with localized nonscarring alopecia.

CONCLUSION

Nonscarring alopecia in SLE is common and correlates with disease activity. Histopathologic and DIF examinations have yielded numerous LE-specific findings, suggesting that the condition is indeed LE specific and may involve a more complex mechanism than that of TE. A majority of patients present with mild diffuse alopecia, but hair loss can also be localized in patches or along the anterior hair line. Common trichoscopic findings were arborizing/interconnecting vessels, blue-grey speckled pigmentation, and thin hypopigmented hair shafts. These examination findings may help elaborate the nonscarring alopecia criteria in the SLICC, leading to more accurate SLE diagnosis in the future.

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