A Retrospective Study of Skin Manifestations in Systemic Lupus Erythematosus and their association with Renal Involvement

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ABSTRACT

Objective: *To identify the types of skin disorders seen in systemic lupus erythematosus (SLE) and to establish the correlation, if any, between cutaneous manifestations, lupus erythematosus (LE) specificity and renal involvement.*

Methods: *The study was a retrospective, descriptive and analytical study conducted at the Dermatology Clinic at the University Hospital of the West Indies. Data were obtained from the medical records of patients diagnosed with SLE and referred to the Dermatology clinic over the period January 2002 to March 2015. Skin disorders were divided into LE-specific, LE-nonspecific and those unrelated to lupus erythematosus based on the Gilliam classification.*

Results: *Thirty-eight patients with skin lesions fulfilled the criteria for SLE diagnosis. The female-to-male ratio was 18:1. Lesions of discoid lupus erythematosus (DLE) were the commonest skin disorder seen and constituted 50% (n = 19) of all lesions. The second most common skin disorders were the malar rash and non-scarring alopecia each of which occurred in 37% (n = 14). Fourteen of the 38 patients had renal disease (37%). Patients with LE-nonspecific skin disease had 6.00 times the odds of developing renal disease (*p *= 0.044, 95% CI: 0.88, 46.41). There was no significant association between specific types of mucocutaneous disorders or the number of different types of skin lesions and renal disease.*

Conclusion: *Lupus erythematosus-non-specific skin disease was associated with increased odds of having renal involvement in SLE. There appeared to be no difference in the prevalence of renal disease in patients with skin manifestations when compared to the overall prevalence in SLE found in other studies.*

Keywords: Mucocutaneous disorders, renal involvement, skin disease, systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which may involve almost every organ in the body. The skin is the second most commonly affected organ after joint involvement. Skin lesions are also the second most frequent way in which the disease presents itself (1). Skin and mucous membrane are involved at some point in the progression of the disease in over 80% of patients. Skin lesions may produce considerable morbidity by causing alopecia, scarring lesions and disfigurement and thereby may produce some degree of vocational handicap in up to 45% of patients (1).

The diagnosis of SLE is based on a combination of clinical features and laboratory findings. The presence of four of the 11 American College of Rheumatology (ACR) criteria yields a sensitivity of 85% and a specificity of 95% for SLE (2). When the Systemic Lupus International Collaborating Clinics (SLICC) group revised the ACR SLE classification criteria in 2012, they classified a person as having SLE in the presence of

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biopsy-proven lupus nephritis with ANA or anti-dsDNA antibodies or if four of the diagnostic criteria, including at least one clinical and one immunologic criterion, have been satisfied (3). The ACR diagnostic criteria in SLE are often presented in a "SOAP BRAIN MD" mnemonic; this corresponds to serositis, oral ulcers, arthritis, photosensitivity, blood disorders, renal involvement, antinuclear antibodies, immunologic phenomena (for example, dsDNA and anti-Smith (Sm) antibodies), neurologic disorder, malar rash and discoid rash.

The classification proposed by the late Professor James Gilliam is the most widely used method of categorization of cutaneous lesions in lupus erythematosus (4). He divided skin lesions into those that were specific and those that were not specific for lupus erythematosus (LE). He further subdivided the category of specific cutaneous lesions into acute, sub-acute and chronic. LE-specific skin diseases include chronic cutaneous, sub-acute cutaneous and acute cutaneous lupus erythematosus (ACLE). Acute cutaneous lupus erythematosus (malar rash) is usually a herald for systemic lupus erythematosus and is almost always associated with underlying visceral involvement. Patients with subacute cutaneous lupus erythematosus (a photosensitive skin eruption which usually lasts longer than ACLE but does not scar) meet systemic lupus erythematosus criteria about 50 per cent of the time, and patients with chronic cutaneous lupus (discoid lupus erythematosus, lupus panniculitis, chilblain lupus, and tumid lupus erythematosus) most often have involvement of the skin alone or predominantly skin disease (5, 6). Lupus erythematosus-non-specific skin lesions are not histopathologically distinct for cutaneous lupus erythematosus (CLE) and may be seen as a feature of another disease process (6). Examples of LE-non-specific skin lesions include: cutaneous vascular disease, non-scarring alopecia, urticaria, non-specific bullous lesions, calcinosis cutis and erythema multiforme. Cutaneous lesions are important in the diagnosis of LE and in determining the prognosis. Skin lesions comprise four of the 11 criteria in the revised ACR criteria for SLE. Patients with LE-non-specific skin manifestations have been shown to have significantly increased disease activity compared to those with only LE-specific lesions and thus tend to require more aggressive therapy and monitoring (7). The number of different skin lesion types is also correlated with disease activity. Skin manifestations specific to LE serve primarily as an important diagnostic indicator (7). Therefore, being able to recognize and categorize cutaneous lesions in SLE are critical for diagnosis, management and determining prognosis. In a Dutch prospective study by Nossent *et al*, 35% of patients with SLE developed lupus nephritis (8). Gilliam *et al* found that 55%, of patients with systemic lupus erythematous had immunoglobulin deposits along the epidermal basement membrane of uninvolved skin (positive lupus band test [LBT]). However, when those with renal disease were compared with those without, it was found that the LBT was positive in 70% of patients with clinical and laboratory signs of renal involvement, but in only 31% of patients who had no renal disease (9). In a study done in France, Huong *et al* found that patients with renal involvement in systemic lupus erythematosus were more likely to have the malar rash (10). The spectrum of skin manifestations in SLE has never been studied in our population. This study endeavoured to investigate whether skin manifestations in systemic lupus erythematosus differed significantly in our population when compared to other populations. Furthermore, we posited that the mechanism of formation of skin disease in SLE is similar to that leading to renal disease and we therefore hypothesised that the prevalence of renal disease in those patients with skin manifestations would be higher than that found in studies of the general SLE populations.

The aims and objectives were: to document the range of skin disorders seen, to record the types of systemic involvement in patients with skin lesions, to investigate any correlation between lupus erythematosus LE-specific and LE-non-specific cutaneous lesions and renal involvement and to establish the correlation, if any, between specific cutaneous lesions and renal disease.

METHODS

Ethical approval was obtained from the University Hospital of the West Indies/The University of the West Indies/Faculty of Medical Sciences, Mona, Ethics Committee. This was a retrospective, descriptive and analytical study. It was done on data from January 2002 to March 2015. Clinic records were used to obtain a list of all patients seen as new patients in the Dermatology Clinic and who were referred with or suspected to have a diagnosis of SLE. Only patients who fulfilled the criteria for diagnosis according to the 2012 revised Systemic Lupus International Collaborating Clinics (SLICC) group were included in the study. Demographic data were obtained from all patients who met the criteria. Results of collagen vascular screens and skin biopsies were noted. Other non-cutaneous organ involvement was recorded. Dermatologic diagnoses were categorized into LE-specific disorders, LE-non-specific disorders

(according to Gilliam's classification) and those unrelated to lupus erythematosus.

The Epi-Data database was used to store the data. Analysis was done using the statistical software STATA version 11. Fisher's Exact Test was used to examine the significance of association (*p*-values) and to calculate 95% confidence intervals because of the small numbers.

RESULTS

Initially 60 subjects were identified. Twenty-two were eliminated as they did not fulfil the diagnostic criteria for SLE. Therefore, analysis was done on 38 patients. Ages at consultation for skin disorders ranged from eight to 66 years with a mean age of 34 years. Ages at diagnosis of SLE ranged from 8 to 58 years with a mean age of 28 years. Thirty-six were female and two were male with a female-to-male ratio of 18:1.

The majority of skin lesions were lupus erythematosus specific (24 patients, 63%). Sixteen patients (42%) had lupus erythematosus non-specific lesions and eight patients (21%) had lesions completely unrelated to lupus erythematosus. These do not add up to 100% as there was overlap; seventeen patients had more than one type of skin disorder.

Lesions of discoid lupus erythematosus (DLE) were the commonest skin disorder seen and constituted 50% (n = 19) of all lesions. The second most common skin disorders were the malar rash and non-scarring alopecia. Both of these occurred in 37% (n = 14). Other mucocutaneous lesions recorded were: oral ulcers, scarring alopecia, vasculitis, pyoderma gangrenosum, photosensitive dermatitis, subacute cutaneous lupus erythematosus (SCLE), lupus profundus, urticaria and dermatitis herpetiformis (Table 1).

Table 1: Types of skin lesions, their frequencies and percentages

Type of skin disorder	Frequency	Percentage
DLE	19	50%
Malar rash	14	37%
Non-scarring alopecia	14	37%
Oral ulcers	8	21%
Scarring alopecia	5	13%
Vasculitis	4	10%
Pyoderma gangrenosum	2	5%
Photosensitive dermatitis	2	5%
Subacute cutaneous lupus	1	2.5%
Lupus profundus	1	2.5%
Lupus profundus	1	2.5%
Dermatitis herpetiformis	1	2.5%

DLE; Discoid lupus erythematosus

Lesions of DLE, malar rash, oral ulcers (DLE type), scarring alopecia, photosensitive dermatitis, SCLE, and lupus profundus were considered LE-specific. The presence of interface dermatitis on histology would distinguish a lesion as being LE-specific. Non-scarring alopecia, vasculitis, pyoderma gangrenosum, urticaria and dermatitis herpetiformis were considered LE-non-specific. There were also cutaneous disorders unrelated to lupus erythematosus. There was one case each of psoriasiform dermatitis, acute spongiotic dermatitis, seborrhoeic dermatitis, condylomata acuminata, striae and post-inflammatory hyperpigmentation. There were two cases of steroid-induced acne.

Of the 38 patients, 21 had arthritis (55%), 14 had renal disease (37%), 11 (29%) had anaemia, four had leukopenia (11%) and four had suffered thrombotic events (11%). There were three cases of cerebral involvement (8%), three cases of serositis including pleuritis and pericarditis (8%), two patients had previously had thrombocytopaenia (5%) and there was one case each of optic neuritis and transverse myelitis (3% each) (Table 2).

Table 2: Non-cutaneous manifestations of systemic lupus erythematosus

Features	Frequency	Percentage
Arthritis	21	55%
Renal disease	14	37%
Anaemia	11	29%
Leukopenia	4	11%
Thrombotic event	4	11%
Cerebritis	3	8%
Serositis	3	8%
Thrombocytopaenia	2	5%
Optic neuritis	1	3%
Transverse myelitis	1	3%

LE; Lupus erythematosus

Analysis was undertaken to first explore the association between LE-specificity and renal disease. For the purpose of analysis, patients were divided into LE-specific lesions and this constituted anyone with LE-specific lesions even if they also had LE-non-specific lesions (Table 3).

Table 3: Categories of LE-specificity used for analysis

Specificity	Frequency	Percentage
LE-specific	24	61%
LE-non-specific only	9	26%
Not related to LE	5	13%
Total	**38**	**100%**

LE; Lupus erythematosus

This group (LE-specific) was compared to those with LE-non-specific lesions only. Patients with "non-specific lesions only" had six times the odds of developing renal disease ($p = 0.044$, 95% CI: 0.88, 46.41). There was no significant difference between those with unrelated skin diseases when compared with LE-specific lesions (OR = 2.00, $p = 0.597$, 95% CI: 0.133, 21.83) (Table 4).

Table 4: Table of odd ratios for LE-specificity and the association with renal disease

Specificity category	Odd Ratio	Fisher test *p*-value	95% CI
LE-specific	1.00		
LE-non-specific only	6.00	0.044	0.88-46.41
Not related to LE	2.00	0.597	0.133-21.83

LE; Lupus erythematosus

Patients were also divided based on the number of different types of skin disorders whether LE-specific or LE-non-specific. The numbers ranged from four to zero. There was no association between the number of types of skin disorders and renal disease ($p = 0.650$).

Further analysis to investigate any association between individual skin lesions or group of lesions and renal involvement was done. When patients with vasculitis were compared to those with no vasculitis, those with vasculitis had an odd ratio (OR) of 6.27 for developing renal disease but this was not statistically significant ($p = 0.132$, 95% CI: 0.42, 343.20). The other skin diseases including discoid rash, oral ulcers, malar rash, scarring alopecia, non-scarring alopecia, pyoderma gangrenosum and photosensitive dermatitis were also not associated with renal disease (Table 5).

Table 5: Skin lesions which show no association with renal disease

Skin Lesion	Fisher's Exact Test *p*-value
Vasculitis	0.132
Discoid rash	0.372
Oral ulcers	1.000
Malar rash	1.000
Scarring alopecia	0.488
Non-scarring alopecia	1.000
Alopecia	0.737
Pyoderma gangrenosum	1.000
Photosensitivity	0.522

DISCUSSION

The female-to-male ratio was higher (18:1) than that found by Kumar *et al* [14:1] (1) for dermatological patients. Both were higher than the female-to-male ratio for SLE (9:1). It could mean that female patients with LE are more likely to have skin manifestations. However, it is possible that women seek dermatological care more readily than men and this healthcare-seeking behaviour (including dermatological care) may vary in different societies. It may also be explained by variations in genetic and racial constitution of the study population leading to variations in the number of females affected by SLE. The higher female-to-male ratio in the present study could be attributed to the findings of Masi *et al* who ascertained that the black female of reproductive age had a significantly increased risk of acquiring and dying from SLE (11). The majority of our country population (93.7%) are of African descent (12) although, race was not included as a variable in this research.

As in the study by Zecević *et al* (7), the present study showed that persons with LE-non-specific lesions were more likely to have renal involvement ($p = 0.044$, 95% CI: 0.88, 46.41). This may support Zecević's findings that although LE-specific lesions are important for diagnosis, LE-non-specific lesions are more important markers of disease activity. It should be noted that no individual type of skin disorder, even those which were LE-non-specific, was shown to be associated with kidney disease.

Renal involvement in our patients was similar to studies of SLE populations with 37% in our study, 35% in the study by Nossent *et al* (8) and 36% in the study by Huong *et al* (10) which both looked at the overall prevalence of renal disease in patients with SLE. This suggests that patients with skin involvement may not be more likely to have kidney disease.

One limitation of our study was the small numbers. Another was its retrospective nature of as there were inconsistencies and variations in the documentation of lesions between different clinicians (which led to difficulty in gleaning some data) and in some cases data from some patients were missing.

CONCLUSION

The major skin disease seen in this clinic in SLE patients was DLE. There was significant increase in the odds of renal disease in patients with LE-non-specific lesions ($p = 0.044$) although there was no association between renal disease and individual mucocutaneous disorders. When compared with the prevalence of renal disease found in other studies of patients with SLE, there appeared to be no difference in the prevalence of renal disease in patients with skin manifestations.

Author Contributions

AD East-Innis originated and designed the paper, supervised and coordinated data collection, conducted data analysis, wrote the manuscript and approved the final version. AS Paolino was involved in the study design, was integrally involved in data collection and approved the final version. KA Stylianou helped in study design, was integrally involved in data collection and approved the final version. KK Clarke participated in study design, assisted with data collected, helped in writing the manuscript and approved the final version. The authors declare that they have no conflicts of interest.

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