Clinico-Pathological Profile of Cutaneous Lupus Erythematosus Patients: A Report from A Tertiary Care Center of Chattogram

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Abstract

Background: Nearly all epidemiologic studies have involved patients with Systemic Lupus Erythematosus (SLE). Few authors have investigated the characteristics of patients with Cutaneous Lupus Erythematosus (CLE). We aim to describe the epidemiologic, clinical, and immunologic characteristics of a series of patients diagnosed with CLE.

Materials and methods: This is a descriptive retrospective cross-sectional study carried out using the register records of total 218 patients attending the ‘Lupus Clinic’ in Chittagong Medical College Hospital during the period 2010 and 2020. The disease activity and damage of CLE were assessed according to the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI).

Results: There were 187 females (86%) and 31 males (14%) with the female: male ratio being 6.1:1. The mean age was 28 ± 10.06 (mean ± SD) ranging between 11 and 65 years. The Chronic Cutaneous Lupus Erythematosus (CCLE) patients accounted 154 (71%) followed by Acute Cutaneous Lupus Erythematosus (ACLE) 46 (21%) and Subacute Cutaneous Lupus Erythematosus (SCLE) 18 (8%). On the basis of CLASI score, 91 (42%) patients were in mild form, 85 (39%) in moderate form and 42 (19%) in severe state. In LE specific skin lesions, common manifestation was photosensitivity 198 (91%) followed by discoid rash 154 (71%) and maculo-papular lupus rash 55 (25%). Oral ulcer was seen in 49 (22%) patients and malar rash in 46 (21%) patients. Other observed LE specific skin manifestations were papulo squamous rash 11 (5%), Toxic epidermal necrolysis like lesions 7 (3%) and lichenoid lesions 6 (3%). Among LE nonspecific skin lesions, common manifestation was non-scarring alopecia 123 (56%) followed by Raynaud’s phenomenon 17 (8%) livedo reticularis 17 (8%) Vasculitis 15 (7%) Periungual telangiectasia 7 (3%) erythema multiforme 6 (3%) and leg Ulcer 5 (2%). Antinuclear Antibody (ANA) 132 (61%) was the most common autoantibody followed by anti-ds DNA 91 (42%) anti-Sm antibody 2 (1%) anti-phospholipid antibodies 9 (4%) and anti-RNP 3 (1%). Hematological manifestations were seen in 161 (73.85%) where erythrocyte sedimentation rate was the most common hematological abnormality 161(73.85%) followed by lymphopenia 126 (57.80%) leucopenia 113 (51.80%) thrombocytopenia 107 (49.10%) anemia 92 (42%) monocytopenia 37 (16.97%).

Conclusions: CCLE was the most common subtypes of CLE. Patients with different subtypes of CLE have distinct clinical and pathological characteristics. The onset or concurrence of SLE mandates the involvement of other disciplines depending on organ involvement. In the absence of consensus on a definition that makes it possible to differentiate cutaneous forms of LE from SLE, the dermatologist’s role in the correct diagnosis and classification of such patients is fundamental.

Key words: Cutaneous Lupus Erythematosus (CLE); Dermatologic manifestation; Skin lesion; Systemic Lupus Erythematosus (SLE).
INTRODUCTION

Cutaneous Lupus Erythematosus (CLE) is a chronic, relapsing autoimmune condition encompassing a wide range of dermatologic manifestations. Skin involvement in CLE patients can be divided into two categories based on histology: Lupus Erythematosus- (LE-) specific and LE-nonspecific skin lesions. The presence of LE-specific lesions is necessary to confirm the diagnosis of CLE. LE-specific skin lesions are divided into several subtypes based on clinical characteristics: Acute CLE (ACLE) Subacute CLE (SCLE) and Chronic CLE (CCLE) with several variants including Discoid LE (DLE) presenting as a localized or generalized form, LE Profundus (LEP) (Also called lupus panniculitis or subcutaneous LE) Hypertrophic LE (HLE) Chilblain LE (CHLE) and Lupus Erythematosus Tumidus (LET)1,2.

Lupus Erythematosus (LE) is a complex autoimmune disease with a worldwide distribution and an unknown etiology3. It is characterized by a great clinical polymorphism and female predominance4,5. The appearance, progression and outcome of LE are influenced by genetic, immunological and environmental factors6. Ethnicity also seems to contribute to the expression and heterogeneity of the clinical and immunological features of disease7. However, few studies have investigated the characteristics of patients with CLE. Most studies of patients with LE have focused on patients with Systemic Lupus erythematosus (SLE) and very few studies have been carried out on the various subtypes of CLE8-12. Epidemiologic data are fundamental to our understanding of the risk and burden of disease in the population. However, such data are challenging and resource intensive to derive in a fragmented health care system and for diseases such as LE, in which a heterogeneous constellation of clinical and laboratory features is necessary to establish a diagnosis. Inadequate data on clinico-pathological manifestations pose a major barrier to further understand this disease. Most of the data available are from the western population. Furthermore, the immune status, individual response to disease and type of antibodies, vary from person to person, place to place and population to population. In this study, we aim to describe the clinical and pathological characteristics of a series of patients diagnosed with CLE who were treated in a specialized unit of a tertiary care teaching hospital of Chittagong, Bangladesh.

MATERIALS AND METHODS

The present investigation is a descriptive retrospective cross-sectional study carried out using the register records of patients attending the ‘Lupus Clinic’ in Chittagong Medical College Hospital (CMCH) during the period 2010 and 2020. CMCH is the oldest tertiary care teaching hospital of the country. The ‘Lupus Clinic’ of CMCH caters for the patients from the Chittagong city as well as from neighboring districts and a multi-disciplinary specialized team is available at the ‘Lupus Clinic’ of CMCH. The patients’ cards were studied and the following clinical data were recorded: demographic characteristics, extent of skin involvement and serological findings were collected. Socio-demographic data included age, sex, completed education, living place (Rural/urban) monthly family income and smoking status.

A total number of 218 inpatients and outpatients with cutaneous involvement during the course of LE were included in the study. Data were obtained by questionnaires filled in by patients during their routine visits to the ‘Lupus clinic’ and by extracting medical records. Diagnosis of CLE has been established based on clinical manifestation and skin biopsy, if necessary. Patients were classified into 3 CLE subtypes: Acute Cutaneous LE (ACLE) Subacute Cutaneous LE (SCLE) or Chronic Cutaneous LE (CCLE) according to Sontheimer and Kuhn et al12,13. The disease activity and damage of CLE were assessed according to the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)14.

The study protocol excluded patients who met the criteria for SLE but did not have LE-specific cutaneous manifestations, and patients who had clinical findings consistent with CLE but whose diagnosis was not confirmed on follow-up. Routine blood, urinalysis, and other biochemical tests were performed. Chest X-ray and echocardiography and electrocardiography were performed in the recommended patients. C3 and C4 levels were measured if needed. Tests for Antinuclear Antibody (ANA) and anti-ds DNA antibodies were performed by Indirect Immunofluorescence Assay (IFA). Autoantibodies to Extractable Nuclear Antigens (ENA) (Sm and Sm/RNP) were studied where applicable by Enzyme-Linked Immunosorbent Assay (ELISA). The IFA and ELISA tests were performed on an automated system.

After collection data were entered into Microsoft Excel spread sheet to generate a master sheet. Then they were fed into Statistical Package for Social Science (SPSS) version 23 for processing and analysis. Descriptive statistics included frequencies, mean, standard deviation, median, minimal, and maximal values. Continuous data were reported as the means ± Standard Deviations (SD) and with regard to categorical ones, we used number and percentages. Proportions were presented with 95% Confidence Intervals (95% CI).

The authors certify that they have obtained all appropriate patient consent forms both in oral and written. The study was conducted in accordance with the Data Protection Act and according to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee at Chittagong Medical College, Bangladesh.

RESULTS

There were 187 females (86%) and 31 males (14%) with the female: male ratio being 6.1:1. The mean age was 28 ± 10.06 (Mean ± SD) ranging between 11 and 65 years. Majority of the patients 142 (65%) were from rural area and 76 (35%) from urban area. Most of the male patients 29 (94%) were smoker (Table I).
Clinico-Pathological Profile of Cutaneous Lupus Erythematosus Patients

### Table I: Demographic characteristics of the patients (n=218)

| Characteristics                  | Frequency (%), (CI) |
|----------------------------------|---------------------|
| Age                              |                     |
| ≤ 18 years                       | 32 (14.7%, 10.3-20.1%) |
| 18-50 years                      | 170 (78.0%, 71.9-83.3%) |
| >50 years                        | 16 (7.3%, 4.3-11.7%)  |
| Sex                              |                     |
| Male                             | 91 (42.2%, 35.4-49.1%) |
| Female                           | 127 (57.8%, 50.9-64.6%) |
| Educational status               |                     |
| Primary                          | 31 (14.2%, 9.9-19.6%)  |
| Secondary                        | 187 (85.8%, 80.4-90.1%) |
| Above Secondary                  | 44 (20.2%, 15.1-26.1%) |
| Smoker                           |                     |
| Male (n=31)                      | 29 (93.5%, 78.6-99.2%) |
| Female (n=187)                   | 1 (0.0%, 0.0-2.9%)    |
| Place of residence               |                     |
| Rural                            | 142 (65.1%, 58.4-71.5%) |
| Urban                            | 76 (34.9%, 28.6-41.6%) |
| MFI (USD)                        |                     |
| < 100                            | 94 (43.1%, 36.6-50.0%) |
| 100-200                          | 65 (29.8%, 23.8-36.4%) |
| >200                             | 59 (27.1%, 21.3-33.5%) |

MFI: Monthly Family Income, USD: U S Dollar CI: Confidence Interval.

Of the 218 patients with CLE, the CCLE patients counted 154 (71%) which was higher than other forms of CLE followed by ACLE 46 (21%) and SCLE 18 (8%).

In LE specific skin lesions, common manifestation was photosensitivity 198 (91%), followed by discoid rash 154 (71%) and maculo-papular lupus rash 55 (25%). Oral ulcer was seen in 49 (22%) patients and malar rash in 46 (21%) patients. Other observed LE specific skin manifestations were papulo squamous rash 11 (5%), Toxic Epidermal Necrolysis (TEN) like lesions 7 (3%) lichenoid lesions 6 (3%). Among LE nonspecific skin lesions, common manifestation was non-scarring alopecia 123 (56%) followed by Raynauds phenomenon 17 (7.8%) livedo reticularis 17 (8%) Vasculitis 15 (6.9%) Periungual telangiectasia 7 (3.2%) erythema multiforme 6 (2.7%) Leg Ulcer 5 (2.3%).

### Table II: Clinical characteristics of skin lesions (Both LE specific and Nonspecific)

| CLE sub types | Frequency (%), (CI) |
|---------------|---------------------|
| ACLE          |                     |
| 46 (21%)      | (0.0-16.7%)         |
| SCLE          |                     |
| 18 (8%)       | (0.0-2.9%)          |
| CCLE          |                     |
| 154 (71%)     | (28-12.8%)          |
| (64.1-76.6%)  | (74.2-98.0%)        |
| LE specific skin lesions | Frequency (%) | Confidence interval |
| Photosensitivity | 198 (90.8%) | 86.2-94.3% |
| Discoid Rash   | 154 (71%) | 64.6-77.0% |
| Maculo-papular lupus rash | 55 (25.2%) | 19.6-31.5% |
| Oral ulcer     | 49 (22.5%) | 17.1-28.6% |
| Malar rash     | 46 (21.1%) | 15.9-27.1% |
| Papulo squamous rash | 11 (5%) | 2.5-8.8% |
| TEN like lesions | 7 (3.2%) | 1.3-6.5% |
| Lichenoid lesions | 7 (3.2%) | 1.3-6.5% |

### Table III: Pathological profile of patients stratified by sex (n=218)

| Variables | Total (n=218) | Sex |
|-----------|--------------|-----|
| Age       | Male (n=31)  | Female (n=187) |
| Male      | 31 (14.2%, 9.9-19.6%) |
| Female    | 187 (85.8%, 80.4-90.1%) |
| MFI (USD) |               |     |
| < 100     | 94 (43.1%, 36.6-50.0%) |
| 100-200   | 65 (29.8%, 23.8-36.4%) |
| >200      | 59 (27.1%, 21.3-33.5%) |
| LE Nonspecific skin lesions | Frequency | Confidence interval |
| Non-scarring Alopecia | 123 (56.4%) | 49.6-63.1% |
| Livedo reticularis | 18 (8.3%) | 5.0-12.7% |
| Raynauds phenomenon | 17 (7.8%) | 4.6-12.2% |
| Vasculitis | 15 (6.9%) | 3.9-11.1% |
| Periungual telangiectasia | 7 (3.2%) | 1.3-6.5% |
| Erythema Multiforme | 6 (2.7%) | 1.0-5.9% |
| Leg Ulcer | 5 (2.3%) | 0.7-5.3% |

Data were expressed as frequency (Percentage) with 95% confidence interval of the proportion.
Abbreviations: ESR: Erythrocyte sedimentation rate, UTP: Urinary Total Protein.

Of the total of 218 patients studied, 132 (61%) patients had positive ANA. Anti-ds DNA antibodies were seen in 91 (42%) patients. Anti-Sm antibodies were found in 2 (1%) patients. Anti-phospholipid antibodies were positive in 9 (4%) and anti-RNP Ab in 3 (1%) patients. Complement 3 (C3) and complement 4 (C4) were decreased in 5 (2%) patients (Table III).

Hematological manifestations were seen in 161 (73.85%) patients. Increased Erythrocyte Sedimentation Rate (ESR) was the most common hematological abnormality followed by lymphopenia 126 (57.80%), leucopenia 113 (51.80%), thrombocytopenia 107 (49.10%) anemia 92 (42%) and monocytopenia 37 (16.97%).
In LE specific skin lesions, common manifestation was photosensitivity 198 (91%), followed by discoid rash 154 (71%) and maculo-papular lupus rash 55 (25%). The prevalence of photosensitivity ranges from 28% to 71%\(^1\). It is one of the major diagnostic criteria for SLE. Photosensitivity precedes the clinical onset of internal manifestations of SLE in about one third of patients. Some patients may not notice erythema after prolonged UV exposure, but hours or days later they may note increased arthralgia, malaise, or fever. CLE is frequently a photosensitive eruption that can be induced by both Ultraviolet A (UVA) and Ultraviolet B (UVB) light. In patients with DLE, SCLE and SLE, the action spectrum of induced lesions was in UVB range in 33%, in UVA range in 14% and in both UVA and UVB in 53%. CLE are photosensitive, therefore, disease prevalence might be higher in areas with more ambient sun exposure. It is important to use both full sleeves clothes and broad spectrum sunscreen and avoidance of both natural and artificial UV light exposures. There is often a latency period of several weeks between UV exposure and disease symptoms so it is important to repeatedly inform the patients about this association\(^2\).

Among LE nonspecific skin lesions, common manifestation was non-scarring alopecia 123 (56%) followed by Raynaud's phenomenon 17 (8%) livedo reticularis 17 (8%) Vasculitis 15 (7%) Periungual telangiectasia 7 (3%) erythema multiforme 6 (3%) leg Ulcer 5 (2%) urticaria 4 (2%) and acanthosis nigricans 2 (1%). On the basis of CLASI score, 91 (42%) patients were in mild form, 85 (39%) in moderate form and 42 (19%) in severe state (Figure-2). Hair loss is a common and characteristic finding in patients with LE. It may be scarring, if preceded by DLE or nonscarring. Urticaria, angioedema, and Raynaud’s phenomenon are common cutaneous vascular reaction patterns. Some patients with LE described lesions suggestive of urticarial vasculitis, with prevalences ranging from 7% to 22%\(^3\),\(^4\). Dermal vasculitis has been reported in 18% to 70% of patients with LE. Livedo reticularis may be associated with the antiphospholipd syndrome and has been reported as an initial manifestation of LE in many patients\(^5\).

Other skin disorders have been occasionally reported in patients with LE, such as erythema multiforme, chronic ulcers, splinter hemorrhages, rheumatoid nodules, and acanthosis nigricans. Mucous membrane involvement was thought to be relatively uncommon in LE. Dubois and Tuffanelli found only a 9% incidence. However, on careful inspection, more than 50% of patients with LE may have mucosal lesions, mainly oral ulcers or nasopharyngeal ulcers.\(^6\). The LE non specific skin manifestations include a wide range of symptoms with different histopathological pictures. The LE non specific skin manifestations are not exclusive to LE disease but are often seen in patients with active SLE but also in several other autoimmune diseases. It is important to screen a patient with CLE for LE non specific symptoms since their presence can imply systemic involvement and progression to SLE\(^7\).

DISCUSSION

Among the patients female 187 (86%) male 31 (14%) with a sex ratio of 6.1:1. The mean age of onset of disease was 28 years (Range 11-65 years). These findings are similar to Indian studies by Kishor N et al and Binoy JP et al where they conducted study on SLE patients\(^1\),\(^2\). Other clinical studies have consistently demonstrated a female predominance also. In general, this percentage ranges from 78% to 96% in most studies, with a female-male ratio of approximately 10:1.\(^3\),\(^4\). This excess of females is especially noteworthy in the 15- to 64-year-old age group, where ratios of age- and sex-specific incidence rates show a 6- to 10-fold female excess. This age related differences in the female-male ratios have been considered to be related to hormonal changes\(^5\). LE can appear in people of any age. It is interesting to note that, in several studies, patient age at the beginning of symptoms can modify the clinical and pathological characteristics of LE.
with LE-nonspecific skin manifestations had significantly increased disease activity compared to those with only LE-specific lesions. The number of different skin lesion types also correlated with disease activity. Patients with only one type of lesion had mild disease. An intermediate disease activity was found in the group with two different lesion types. ACLE has a strong association with systemic disease and non-specific skin lesions always indicate disease activity.

The high incidence of CLE emphasizes the importance of following up these patients and recognizing the clinical presentation of disease. Although the cutaneous form of LE has a more indolent course, monitoring the patient’s disease is still essential because the disease in some cases progresses to the systemic form, which has a drier prognosis. Early recognition of CLE by the physician translates to early management and, hopefully, to preventing transition of the disease to the systemic form. CCLE and SCLE last for many years and may lead, like SLE, to severe work-related disability and limited life quality. Also, in a small proportion of patients with CLE, SLE develops during the course of their disease, which implies a considerable amount of medical management and costs for the community.

Early recognition of patients with CLE who are at risk for SLE development and preventive measures against disease-triggering factors are important tasks for physicians of patients with CLE. Signs of nephropathy, elevated antinuclear antigen triggering factors are important tasks for physicians of patients with CLE. The high incidence of CLE emphasizes the importance of identifying SCLE, ACLE patients with often relatively minimal systemic involvement tends to be mild in most patients with CLE, the disease has a major impact on quality of life because the lesions are usually located on the face and the chronic forms can cause irreversible scarring. Moreover, up to 28% of patients with CCLE are susceptible to developing SLE. The different types of CLE share similar and overlapping pathological features to a greater or lesser extent. There is controversy as to whether SLE and CLE represent different spectrum of the same disease or are distinct disease phenotypes. CLE is an exemplar of a disorder requiring a multidisciplinary approach for its management. It has the potential to intersect with many disciplines and each can contribute to providing the optimum outcome for patients. The disciplines range from the basic sciences through to different organ-specific clinical specialties.
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