Case Series

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Dermatology Section

A Case Series of Cutaneous Lupus Erythematosus Progressing to Systemic Lupus Erythematosus in a Lightning Phase

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ABSTRACT

Discoid Lupus Erythematosus (DLE) is a chronic, disfiguring, inflammatory skin disease characterised by erythematous, indurated, well-defined scaly plaques of varying sizes that resolve with atrophy, scarring, and pigmentary changes. Although discoid cutaneous lesions are typical of DLE, they are also seen in as many as 14% of patients with Systemic Lupus Erythematosus (SLE). The aetiopathogenesis of Cutaneous Lupus Erythematosus (CLE) is thought to be related to the same autoimmune abnormality responsible for the systemic components of LE. The key feature in the pathogenesis being upregulation of Interferon-α (IFN-α) signaling. Hence, the morphology and associated clinical features of DLE can be considered as a forerunner in assessing the development of SLE. This case series highlights some potential risk factors to watch out for in the progression to SLE in patients with DLE. Some parameters that are likely to predict early progression towards SLE from DLE are: early age at diagnosis (<25 years), female gender (2:1), Fitzpatrick skin type V and VI, presence of disseminated DLE lesions, arthralgia, anaemia (Hb-<10 g/dL), lymphopenia (lymphocyte count-<20%), isolated lesions at photoprotected sites, average disease duration ranging from 5.7 to 8 years, elevated ESR, high baseline ANA titres ≥1:320, anti-ds-DNA, anti-SS-A, and anti-Sm antibody positivity. Hence, assessment of the above-mentioned parameters in initial and follow-up visits might aid in the early diagnosis of SLE. This case series consists of four patients (33 years old female, 54 years old female,34 years old female and 49 years old male patients, all married), all of whom had multiple potential risk factors indicating rapid progression towards the development of systemic symptoms. Hence, this shifts the prior paradigm that DLE patients do not typically develop severe SLE. Risk score analysis may be a helpful tool in assessing ongoing subclinical inflammation and aiding in the early diagnosis of SLE. Appropriate therapeutic intervention could be key in stemming disease progression, reducing morbidity and mortality, and improving the patient's quality of life.

Keywords: Chronic inflammation, Disease progression, Prediction model, Risk factors, Systemic symptoms

INTRODUCTION

Lupus erythematosus is an autoimmune disease that may present as a limited skin disease, such as CLE, or systemic disease with manifestations ranging from biological abnormalities or mild symptoms to a potentially life-threatening disease with multiorgan involvement, as in SLE [1,2]. Among CLE cases, DLE is the most common subtype and accounts for approximately 80% of cases [3]. At the time of diagnosis, the majority of patients with DLE do not have associated SLE; however, some of them will develop SLE during the follow-up period. Untreated SLE is often progressive and has a significant fatality rate [4,5]. Past reports have suggested that the cross-sectional prevalence of SLE ranges between 5-15% [6] among patients with localised DLE (present in one region of the body) and 20-25% among patients with more generalised DLE, thus highlighting the importance of regular follow-up and thorough examination of DLE patients [7,8].

Widespread DLE lesions, arthralgia, nail changes, anaemia, leucopenia, high erythrocyte sedimentation rates, and high titres of Antinuclear Antibodies (ANA) have been identified as potential risk factors for progression from DLE to SLE [5,9]. However, there is currently no standard prediction tool or criteria to assess the factors that determine DLE to SLE progression.

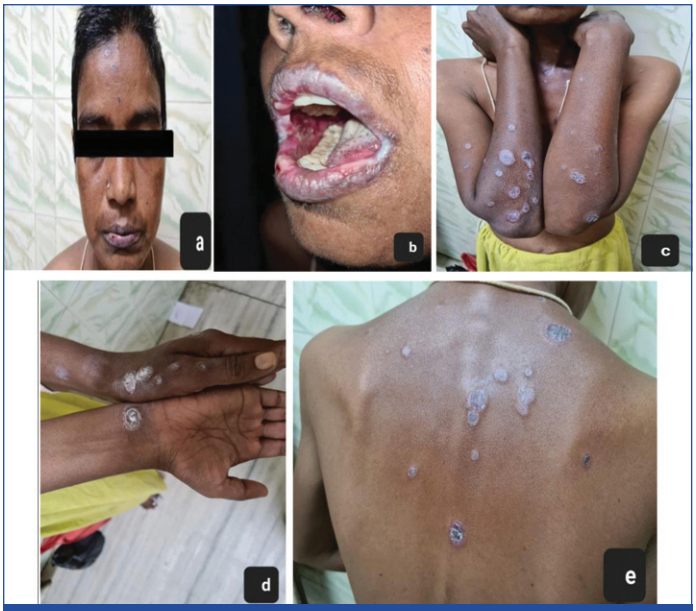
This case series is an attempt to highlight the risk factors and generate a predictive score for progression to SLE among patients with isolated DLE. All patients aged above 18 years, who were either known or suspected cases with cutaneous symptoms of lupus erythematosus, including DLE, ACLE, or SCLE, are presented in this case series.

Case 1

A 33-year-old married female patient from Chennai presented to the Dermatology OPD with complaints of high-grade fever, hyperpigmented scaly lesions all over the body, and painful oral erosions for the past 15 days. She also had photosensitivity, myalgia, arthralgia, conjunctival congestion, and increased hair loss for the past year. The patient is a known case of subacute CLE for the past year and is on regular follow-up in our institute. She also gave a history of prior admission for an episode of seizure and pedal oedema six months after the initial diagnosis, and a past history of two spontaneous abortions eight years ago. She was thin-built, had pallor, and had a Fitzpatrick skin type of 5.

Dermatological examination showed multiple well-defined annular and polycyclic pigmented scaly macules and patches of varying size over the forehead, neck, extensor aspect of forearms, upper and lower back, and dorsum of hands and feet. Erosions were noted over the buccal mucosa, gingiva, and lips [Table/Fig-1]. Mild conjunctival congestion of the right eye with epiphora and diffuse thinning of scalp hair were also noted.

Haematological evaluation showed haemoglobin within the normal range (12.8 g/dL), an elevated ESR, and a lymphocyte count of 13.4%. ANA (IgG) was assessed by ELISA, which was positive with a titre of 1:100 fine speckled pattern. Anti-dsDNA was positive with a titre of 196 IU/mL, anti-Smith antibody was positive 3+, and anti-histone antibody was positive 1+. Although her risk score based on the prediction model was one, she had nine potential risk factors indicating progression towards SLE.



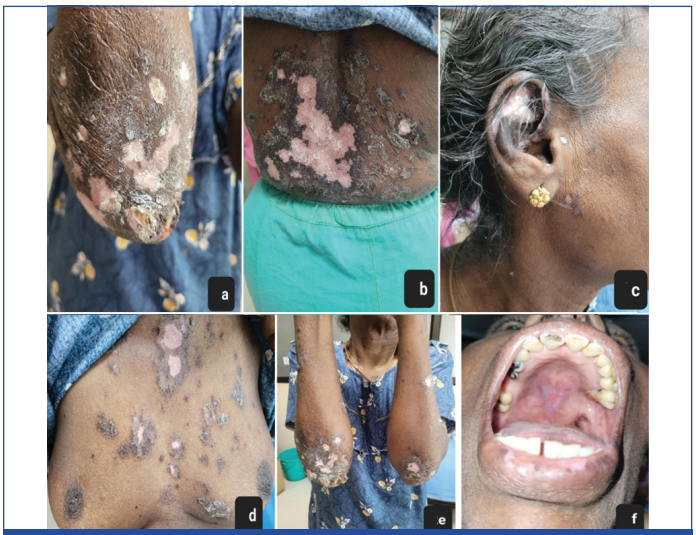
[Table/Fig-1]: Annular and polycyclic pigmented scaly macules and patches over the forehead (1a); Erosions over the buccal mucosa, gingival and lips (1b); Annular scaly plaques over elbows (1c); extensor aspect of forearms (1d); neck, upper and lower back (1e).

She was diagnosed as a case of SLE and given injection Dexamethasone 2cc daily for 10 days, which was later tapered down to oral steroids along with supportive care. After treatment, she showed improvement and was followed-up every two weeks. The patient is currently taking tablet Hydroxychloroquine 200 mg HS.

Case 2

A 54-year-old married female patient presented with complaints of erythematous raised skin lesions, arthralgia, and photosensitivity on and off for the past month. She is a known case of disseminated DLE for the past year and has been on regular follow-up. She is also a known diabetic on medication since two years. On examination, she appeared pale, moderately built, and had bilateral pitting pedal oedema. She had a Fitzpatrick skin type of 5.

Dermatological examination revealed multiple well to ill-defined erythematous scaly plaques with central depigmentation and a peripheral hyperpigmented rim. The size of the plaques ranged from 3×3 cm to 10×10 cm were noted over the ears, face, chest, back, both upper limbs, right knee, and left thigh. The lesions on the elbows showed minimal surface erosion and crusting. Shuster sign was positive and a single healing ulcer was noted over the hard palate [Table/Fig-2].



[Table/Fig-2]: Erythematous scaly plaques with central depigmentation and peripheral hyperpigmented rim over right elbow (2a); lower back (2b); right ear with Positive Shuster sign (2c); chest (2d); B/L elbows (2e); single healed ulcer over the hard palate (2f).

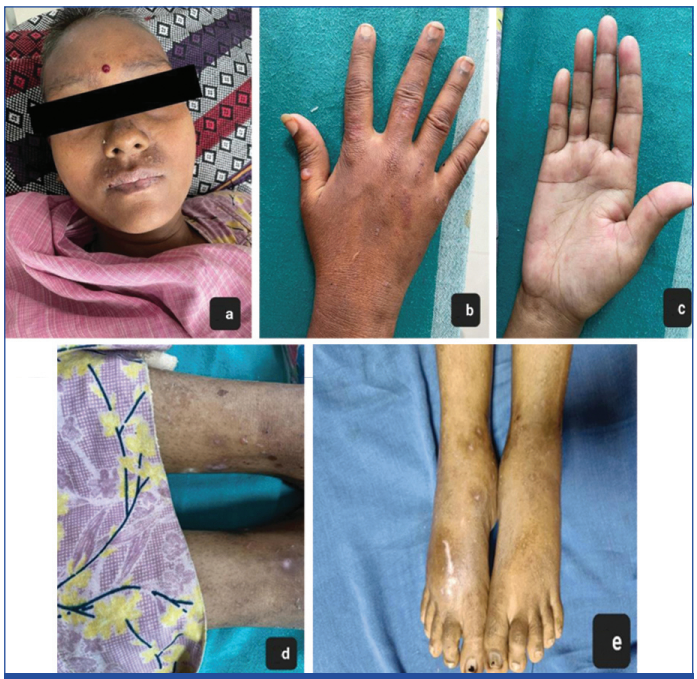
Routine laboratory investigations showed anaemia (haemoglobin-8.7 g/dL), lymphopenia (20%), positive ANA (Hep2) titres with a 4+ speckled pattern, positive anti-dsDNA (594.3 IU/L), increased 24-hour urine protein (936 mg/day), and low complement levels (C3 -0.149, C4- 0.047).

The risk score of this patient was one based on the prediction model, but she had 10 potential risk factors. Hence, the diagnosis of disseminated DLE progressed to acute onset SLE and she was immediately intervened with Injection Methylprednisolone pulse 1 gram i.v. for three days, followed by tapering down to oral steroids within two weeks. The patient is being followed-up once every two weeks regularly.

Case-3

A 34-year-old married female patient presented with complaints of multiple blisters over the hands and feet associated with itching, arthralgia, photosensitivity, and pedal oedema for the past day. She was a known case of CLE and dilated cardiomyopathy with failure for the past year. On examination, she was moderately built, had pallor, and had a Fitzpatrick skin type of 4. She had palmar telangiectatic erythema and bilateral pitting pedal oedema, indicative of an acute flare-up of disease activity.

Dermatological examination she had resolved ill-defined erythematous plaques with minimal scaling, central depigmentation, and a peripheral hyperpigmented rim. The size of the plaques ranged from 1×1 cm to 2×2 cm and they were present over the face and lower legs. A few intact tense bullae with clear fluid were noted over the dorsum of both hands and ankles, and a single healed erosion was noted over the hard palate [Table/Fig-3].



[Table/Fig-3]: Ill-defined plaques with minimal scaling, central depigmentation and peripheral hyperpigmented rim over the face (3a); few intact tense bulla of size 1*1cm with clear fluid was noted over the dorsum of right hand (3b); palmar telangiectasia (3c); intact bulla on the lower legs (3d); pedal oedema (3e).

On further work-up, her haemoglobin was found to be 10 g/dL, lymphocyte count was 20%, ANA by indirect immunofluorescence was positive with a titre of 1:100 and a 3+ granular pattern. Anti-dsDNA was positive (586 IU/mL), anti-histone antibody was positive (3+), and anti-U1 RNP, anti-Sm, and anti-nucleosome antibodies were also positive.

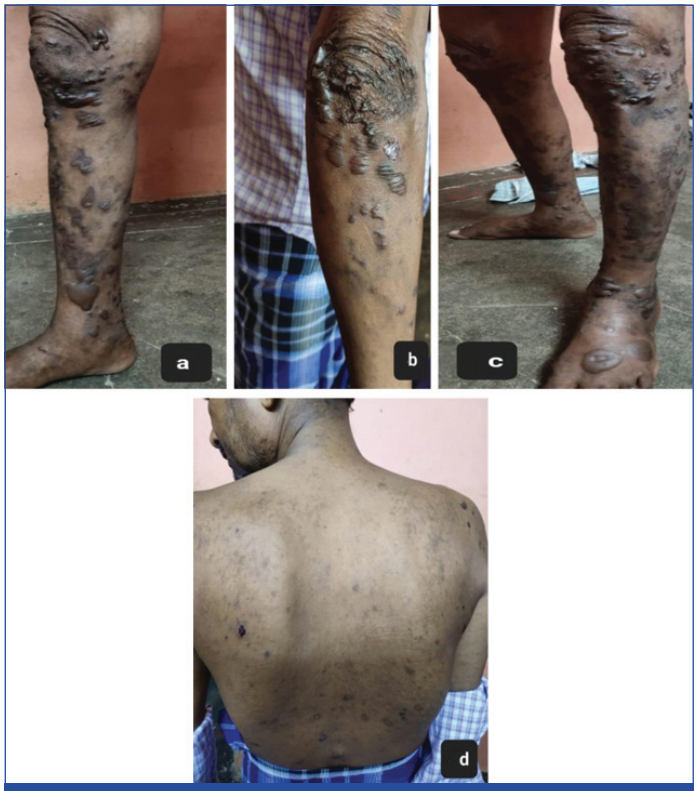
The risk score of this patient was 0 based on the prediction model, but she had 10 potential risk factors. Considering the rapid occurrence of bullous lesions over the photoprotected sites, concurrent pedal oedema, and the nature of the cutaneous and mucosal lesions, a diagnosis of CLE with mucocutaneous

flare/Bullous SLE/Dilated Cardiomyopathy not in failure was made. Nephrologist opinion was sought, and subsequent renal biopsy was done, with the reports consistent with class 4 Lupus nephritis. The patient received three pulses of Inj. i.v. cyclophosphamide as per the NIH Protocol, showed a drastic response, and is currently under regular follow-up.

Case 4

A 49-year-old married male patient, who had been treated for the past year as a case of Herpetic gingivostomatitis/pemphigus vulgaris in a private hospital, presented with complaints of high-grade fever, fluid-filled lesions all over the body, and painless oral lesions for the past 10 days. He also had oral erosions, myalgia, arthralgia, and conjunctival congestion. On examination, the patient was moderately built, had pallor, and had a Fitzpatrick skin type of 5.

Dermatological examination revealed multiple haemorrhagic and fluid-filled vesicles and bullae ranging in size from 0.5×0.5 cm to 5×5 cm over the trunk, lower and upper limbs, and gluteal region [Table/Fig-4]. Multiple erythematous erosions were noted over the hard palate.



[Table/Fig-4]: Multiple haemorrhagic and fluid filled vesicle and bulla of size ranging from 0.5*0.5 cm to 5*5 cm on lower leg (a), both upper limbs (b), another lower limb (c) and over the trunk (d).

Considering his clinical presentation and history, a provisional diagnosis of Bullous SLE was made. Further evaluation showed that the patient was anaemic (Hb-6.8 g/dL), had leucocytosis (WBC-15,000 cells/mm^3), and had alarmingly high serum urea and serum creatinine levels (130 mg/dL and 4.6 mg/dL, respectively). ANA (Hep 2) was negative, while anti-dsDNA was positive (122.2 IU/mL).

The risk score of this patient based on the prediction model was 0, but he had 6 potential risk factors indicating progression towards SLE. It is worth mentioning that the initial presentation itself was with Bullous SLE and end organ damage. The patient was immediately started on parenteral steroids given over a span of two weeks, followed by oral steroids and four cycles of dialysis. He is currently under regular follow-up.

The clinical presentation and laboratory investigations are summarised in [Table/Fig-5]. While the risk score comparison based on the parameters for all four cases are shown in [Table/Fig-6].

S. No.	Parameter	Case 1	Case 2	Case 3	Case 4
1	Age at diagnosis	33	54	34	49
2	Sex	F	F	F	M
3	Fitzpatrick skin type	V	V	IV	V
4	Disease duration	6 months	6 months	12 months	5 months
5	Lesions localised/ disseminated	Disseminated	Disseminated	Disseminated	Disseminated
6	Lesion at photoprotected site	+	+	+	+
7	Arthalgia	+	+	+	+
8	Anaemia	12.8 g/dL	8.7 g/dL	10 g/dL	6.8 g/dL
9	Lymphopenia	13.4%	20%	20%	22%
10	Elevated ESR	+	+	+	+
11	Baseline ANA	1:100	+	1: 100	-
12	Anti-ds-DNA	196 IU/L	594.3 IU/L	586 IU/L	122.2 IU/L
13	Anti-smith Ab	3+	-	3+	-
14	Anti-SS-A Ab	-	-	-	-

[Table/Fig-5]: Summary of the case series and potential risk factors.

Parameter	Case 1	Case 2	Case 3	Case 4
Risk score	1	1	0	1
Number of potential risk factors	9	10	10	6

[Table/Fig-6]: Parameters and corresponding scores.

DISCUSSION

Discoid Lupus Erythematosus (DLE) is a chronic inflammatory skin disease that is the most common form of Cutaneous Lupus Erythematosus (CLE). It is characterised by erythematous, indurated, well-defined scaly plaques of variable size that resolve with atrophy, scarring, and pigmentary changes. Follicular involvement is a prominent feature of DLE [1,2].

Systemic Lupus Erythematosus (SLE) is an episodic multisystem autoimmune disease characterised by widespread inflammation of blood vessels and connective tissues. It is diagnosed based on the presence of at least 4 of the 11 American College of Rheumatology criteria, which include malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurological disorder, hematological disorder, immunologic disorder, and positive ANA [10]. The clinical manifestations are extremely variable, and the disease course is unpredictable.

The pathogenesis of cutaneous lupus erythematosus is closely linked to the pathogenesis of SLE. It is believed to be due to the interaction between genetic, environmental, and retroviral factors that lead to loss of self-tolerance [11].

While some cases of SLE present directly, a significant proportion of patients progress from cutaneous lupus erythematosus to SLE, with the initial presentation being disseminated DLE, subacute CLE, or localised acute CLE. thus stressing the importance of long-term and regular follow-up for these patients. Despite advancements in diagnosis and treatment for SLE, there is no universally accepted protocol or scoring tool to assess the progression from CLE to SLE. Neither ARA and SLICC, are not able to effectively distinguish between patients with exclusive cutaneous involvement and those with the potential for organ involvement [9].

Risk factors for progression to SLE include the presence of subacute CLE or acute CLE skin lesions, diffuse non-scarring alopecia, non-specific skin lesions such as vasculitis, periungual nail fold telangiectasia, Raynaud phenomenon, generalised lymphadenopathy, unexplained anaemia, marked leucopenia, false-positive tests for

syphilis, hypergammaglobulinemia, elevated erythrocyte sedimentation rate (especially >50 mm/hour), persistently positive high-titre ANA assay, anti-single stranded DNA antibody, positive lupus band test, and high levels of soluble IL-2 receptor [5].

This case series was conducted to emphasise the importance of assessing certain baseline parameters at the initial and subsequent visits of patients with exclusive cutaneous involvement in order to aid in the early diagnosis of SLE. The analysed parameters were obtained from various retrospective studies, as there is no established protocol for assessing the progression of CLE to SLE.

A retrospective hospital registry-based study by Curtis P et al., identified three high-risk parameters: age of CLE diagnosis ≤25 years (1 point), Fitzpatrick skin type V and VI (1 point), and baseline ANA titres of 1:320 (5 points). The study concluded that the average duration of disease progression from DLE to SLE was 5.7 years [11]. Fredeau L et al., stated that individuals with a total score of 6 or more at the initial evaluation had a 40% risk of developing SLE [9]. Based on other literature [12,13], 11 additional potential risk factors were identified to play a vital role in disease progression [14].

Although organ involvement can be identified based on certain clinical symptoms, signs, and elevated autoantibody titres, the lack of a definitive protocol makes it challenging for physicians to classify a CLE patient as SLE. It is noteworthy that, despite regular follow-up, all four patients in the present study rapidly progressed from cutaneous involvement to frank end organ damage within a relatively short period of 5 to 12 months. Although the present study has a smaller sample size, it has minimal inter-observer bias as the majority of patients were assessed by the same set of physicians in our lupus clinic. This case series aimed to highlight all the clinical and laboratory parameters that act as potential risk factors in disease progression, as early diagnosis and appropriate therapeutic intervention is the ultimatum in the management of SLE.

CONCLUSION(S)

Disseminated discoid cutaneous lesions, which are typical of DLE, can be observed in upto one-quarter of patients with SLE. This could be attributed to the shared aetio-pathogenesis of CLE and SLE, which involves abnormal upregulation of the IFN-α signaling pathway. In this series, a rapid progression from CLE to SLE was observed, with an average duration of 5 to 12 months from the time of diagnosis. Although all patients had a risk score of one, most of them had multiple potential risk factors ranging from 6 to 10. This highlights the importance of early diagnosis and timely intervention, which can significantly impact the management of SLE.

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