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Full Length Research Paper

Discoid lupus erythematosus: Description of 130 cases and review of their natural history and clinical course

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Discoid lupus erythematosus (DLE) is one of the most common forms of cutaneous lupus erythematosus (CLE). The purpose of this study was to evaluate the clinical manifestations, laboratory findings and the natural course of Thai patients with DLE, as well as the factors that may incline DLE patients to develop systemic lupus erythematosus (SLE). We retrospectively studied 130 patients with DLE between January 2002 and December 2007. Seventy-six patients (58%) presented with a localized form of classic DLE with the primarily involved location on the face (52.3%). Fifty-nine of 130 patients (45.4%) fulfilled American College of Rheumatology criteria for SLE. Twenty-seven of 59 patients (45.7%) had DLE which preceded the diagnosis of SLE. Among these patients, 50% would progress to develop SLE 2 years from the disease onset. In our study, the presence of antinuclear antibodies (ANA) had the highest statistical relevance for distinguishing between those patients with only DLE lesions and those who would transit into SLE. Seventy one patients (54.6%) had only cutaneous lesions without fulfilling the criteria of SLE even after long-term follow up. Comparing with Caucasians' data, our study revealed a higher percentage of positive ANA, less frequency of photosensitivity but more progression to SLE even with the same risk factors.

Key words: Discoid lupus erythematosus, natural history, clinical course.

INTRODUCTION

Cutaneous lupus erythematosus (CLE) is the second most common clinical finding of LE after rheumatologic manifestation (Costner et al., 2008). In many patients, it diminishes their quality of life and increases a disability of work (Tebbe et al., 1997). LE patients may have only cutaneous symptoms or those in association with systemic involvement (Sontheimer and McCauliffe, 2007). CLE had more favorable prognosis than systemic LE (SLE) (Tebbe, 2004). CLE can be divided into 3 types; acute, sub-acute and chronic (Gillium and Sontheimer, 1981).

Previous studies showed that 35 - 60% of patients with acute CLE (ACLE) had systemic involvement and the exacerbation of cutaneous symptoms correlated with major organ involvement, (Sontheimer and McCauliffe, 2007; Costner et al., 2008) while up to 50% of patients with sub-acute CLE (SCLE) may develop systemic involve-ment (Tebbe, 2004; Sontheimer and McCauliffe, 2007). Chronic CLE (CCLE), the most common one, was reported to be associated with systemic involvement in between 15 - 30%. Callen reported that only 5% of patients with localized DLE developed SLE, but 25% of patients with widespread DLE developed SLE (Callen, 1982). Twenty-four percent of 34 patients diagnosed as childhood DLE had systemic involvement (Sampaio et al., 2008).

Many factors were reported to influence the development of CLE such as sex, race, age, genetic and external factors. There was a report of immunogenetic differences between Oriental and Caucasian populations result in differences in the clinical presentation and frequency of auto anti-bodies detected in some autoimmune diseases (Nishikawa and Provost, 1991). As far as we knew, there were only two small studies of DLE

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Abbreviations: DLE, Discoid lupus erythematosus; **CLE,** cutaneous lupus erythematosus; **SLE,** systemic lupus erythematosus; **ANA,** antinuclear antibodies.

in Asian populations (Ng et al., 1985; Tang et al., 1996).

The purpose of our study was to assess clinical manifestations, laboratory findings, the natural course of Thai patients with DLE, and also the factors that may attribute DLE to the development of SLE, whose data might be one of the representative large bodies of data from Asiatic populations.

MATERIALS AND METHODS

This study was approved by Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University. We retrospectively reviewed case record of 130 patients diagnosed as DLE who attended the outpatient autoimmune clinic, Department of Dermatology, Siriraj hospital, Bangkok, Thailand, between January 2002 and December 2007. The diagnosis of DLE was made on the basis of clinical grounds by dermatologists and was confirmed by histopathologic and direct immunofluorescence (DIF) study (Sontheimer and McCauliffe, 2007). Classic DLE (Figure 2) is characterized by well demarcated, coin-shaped, erythematous plaque with adherent scales, follicular plugging, telangiectasia and peripheral hyperpigmentation. Older lesions have central hypopigmented atrophic area, scars or prominent pigmentary changes. Such lesions are classified into localized form that occurs only on the head and neck region and generalized form that occurs both above and below the neck. Hypertrophic DLE shares clinical features with classic DLE except exaggerated hyperkeratosis (Sontheimer and McCauliffe, 2007; Costner et al., 2008). Histopathologic criteria for diagnosis of DLE are as followings; stratum corneum hyperkeratosis and follicular plugging, hydropic degeneration of basal cells, basement membrane thickening, lymphocytic infiltration along the dermo-epidermal junction (DEJ) and appendages, interstitial mucin deposition (Winfield and Jaworsky, 2009). DIF patterns were interpreted according to standard criteria (Valenzuela et al., 1984). Positive DIF studies were those with granular immunoreactant deposits at the DEJ. Others included deposits at colloid bodies, dermal blood vessels and epidermal nuclei (Kulthanan et al., 1996).

The following data were collected: demographic data, history and physical examination, laboratory investigations included complete blood count, urinalysis, antinuclear antibodies (ANA) which are detected by the indirect immunofluorescense technique using Hep-2 cells as substrates, and erythrocyte sedimentation rate (ESR) and other investigations that were necessary for the individuals, treatment and disease outcome. Patients were classified as having SLE according to the American College of Rheumatology revised criteria (Tan et al., 1982).

Statistical analysis

Descriptive statistics, such as mean, median, minimum, maximum and percentages, were used. The disease progression and time developed to SLE was analyzed by using Kaplan-Meier survival curve. All statistical data analyses were performed using SPSS for Windows version 10.0.

RESULTS

One hundred and thirty patients with skin biopsy proved of DLE were enrolled. One hundred and nine patients (84%) were female and 21 (16%) were male, with the female to male ratio of 5:1. The mean (SD) age of onset was 36 (14.3) years old with a range of 8 - 69 years. There were no patients with family history of DLE. However, two patients had family history of SLE. Seventy-six patients (58%) presented with a localized form of classic DLE which was limited to the head and neck, while generalized lesions of classic DLE were observed in 54 patients (41.5%). The majority of patients presented with clinically characteristic lesions of DLE with the primarily involved location on the face (52.3%) (Table 1). Hypertrophic DLE was detected in two cases (1.5%). DIF study had been performed in 86 patients with the positive result in 58 patients (67.4%); mostly granular immunoreactant deposits at the DEJ (66 cases, 66.3%). Others included deposits at colloid bodies (26 cases, 30.2%), dermal blood vessels (9 cases, 10.5%) and epidermal nuclei (1 case, 1.2%).

Table 1. Demographic data of patients with discoid lupus erythematosus (DLE) (n = 130).

Characteristics	Number (%)
Sex	
Male	21 (16)
Female	109 (84)
Family history of DLE	0
Family history of SLE	2 (1.6)
Localized DLE	76 (58.4)
Generalized DLE	54 (41.5)
Location	
Face	68 (52.3)
Scalp	23 (17.7)
Ear	11 (8.5)
Arms	10 (7.7)
Lip	9 (6.9)
Trunk	5 (3.8)
Others	4 (3.1)

*SLE: Systemic lupus erythematosus

Table 2 shows other clinical manifestations that also were detected in our patients with DLE. Malar rash, photosensitivity, and oral ulcer were the three most common findings; they are criteria for SLE diagnosis. Table 3 shows laboratory abnormality in our patients with DLE. ANA were detected in 89 of 129 patients (69%), mostly at high titers. Speckled pattern was the most common pattern seen (60 in 89 cases; 67%).

Hematologic involvements particularly lymphopenia and leukopenia were detected in 31 patients (23.8%). Eighteen out of 130 patients had abnormal urinalysis, mostly proteinuria. Rising of serum creatinine (more than 2) was detected in 5 of 25 patients (20%).

Fifty-nine out of 130 patients (45.4%) were diagnosed with SLE. Among these 59 patients, 17 patients (28.8%)

Table 2. Other manifestations detected in our patients with DLE.

Manifestations	Number (%)		
	Male (n = 21)	Female (n = 109)	Total (n = 130)
Malar rash	1(4.8)	20(18.3)	21(16.2)
Photosensitivity	3(14.6)	16(14.7)	19(14.6)
Oral ulcer	2(9.5)	15(13.8)	17(13.1)
Vasculitis	0	14(13.9)	14(10.8)
Raynaud's phenomenon	0	3(2.7)	3(2.3)
LE profundus/ LE panniculitis	1(4.8)	2(1.8)	3(2.3)
Subacute cutanous LE	1(4.8)	2(1.8)	3(2.3)
Periungual telangiectasia	1(4.8)	2(1.8)	3(2.3)
Bullous SLE	0	1(0.9)	1(0.8)
Tumid LE	0	1(0.9)	1(0.8)
Urticarial vasculitis	0	1(0.9)	1(0.8)
Livido reticularis	0	1(0.9)	1(0.8)
Digital pitted scar	0	1(0.9)	1(0.8)
Sclerodactyly	0	1(0.9)	1(0.8)

Table 3. Laboratory abnormalities in DLE patients (n = 130).

	Male	Female	Total
	Number	Number	Number (%)
Positive ANA	12	77	89(68.5)
CBC	3	28	31(23.8)
Anemia(Hb < 10 g/dL or Hct < 30%)	0	6	6(4.6)
Positive Coomb's test	0	2	2(1.5)
Leukopenia (WBC < 4,500 cell/µL)	0	8	8(6.1)
Lymphopenia (lymphocyte < 1,500 cell/µL)	1	13	14(10.8)
Thrombocytopenia (platelet < 100,000 cell/µL)	0	1	1(0.8)
Positive serum immunologic disorder			
Anti ds DNA	0	23	23(17.6)
Anti Sm	0	4	4 (3)
ESR (> 20 mm/h)	3	16	19(14.6)
Abnormal urinalysis	1	17	18 (13.84)
Persistent proteinuria	1	14	15(11.5)
Cellular casts	0	3	3(2.3)

were diagnosed as SLE before DLE developed; in 15 patients (25.4%), SLE and DLE were simultaneously diagnosed; in 27 patients (45.7%), DLE preceded the diagnosis of SLE. Seventy-one patients (54.6%) had only cutaneous lesions without the fulfillment of criteria of SLE even after long-term follow up (mean time follow up to 5 years). Table 4 shows the predictive factors for patients with DLE at risk to develop SLE, using a univariate analysis. The following parameters were identified as significantly parameters for patients with DLE who would develop SLE: generalized DLE lesions, photosensitivity, malar rash, abnormalities in CBC and urinalysis, and the presence of ANA and anti-dsDNA ($p < 0.05$).

Our study showed that the presence of ANA had the highest statistical relevance for distinguishing between those patients with only DLE lesions and those who will transit into SLE (Hazard ratio; HR = 3.29, confidence interval; CI = 1.04 - 10.44). It was followed by abnormal urinalysis, the presence of rheumatologic symptoms such as arthralgia and arthritis, and generalized DLE lesions (Table 5).

Figure 1 shows a Kaplan-Meier curve demonstrating duration of the disease and probability of developing to SLE among DLE patients who developed SLE (n = 27).

Table 4. Predictive factors for patients with DLE at risk to develop SLE (univariate analysis).

Parameter	Number of patients	Number of new SLE patients	Median time (month)	P value (Log-rank test)
CBC abnormalities				
Absent	99	20	-	< 0.001
Present*	31	22	32	
ANA				
Absent	40	6	-	
Present*	89	36	96	0.001
Photosensitivity				
Absent	102	26	120	
Present*	28	16	24	0.002
Abnormal urinalysis				
Absent	112	32	120	
Present*	18	10	96	0.004
DLE				
Localized	76	14	120	0.007
Generalized*	54	28	60	
Anti-dsDNA				
Absent	107	28	120	0.007
Present*	23	14	36	
Malar rash				
Absent	109	31	120	
Present*	21	11	24	0.044
Oral ulcer				
Absent	97	28	120	
Present	33	14	108	0.124
Rheumatologic manifestations				
Absent	107	28	120	
Present	23	14	108	0.124
Sex				
F	109	38	96	0.148
M	21	4	108	
ESR				
Absent	111	38	77	
Present	19	4	11	0.278
Vasculitis				
Absent	116	36	108	
Present	14	6	120	0.287

*: $p < 0.05$

Table 5. Multivariate analysis of selected risk factors of DLE progress to SLE.

Characteristics	Coefficient	Standard error	*P-VALUE*	Hazard ratio	Confidence interval
Positive ANA*	1.190	0.589	0.043	3.288	1.04 - 10.44
Abnormal urinalysis*	0.996	0.508	0.050	2.708	1.01 - 7.32
Presence of rheumatologic manifestation*	0.979	0.377	0.009	2.662	1.27 - 5.57
Generalized DLE lesions*	0.766	0.379	0.043	2.150	1.02 - 4.52
Photosensitivity	0.661	0.370	0.074	1.938	0.28 - 1.68
Rising serum creatinine	0.619	0.728	0.395	1.857	0.446 - 7.74
Malar rash	0.540	0.480	0.261	1.715	0.67 - 4.40
Abnormal CBC	0.442	0.373	0.235	1.55	0.75 - 3.23
Positive anti-ds DNA	0.337	0.390	0.388	1.400	0.652 - 3.01
Female sex	0.018	0.571	0.975	1.018	0.33 - 3.12
Age	0.04	0.014	0.776	1.004	0.98 - 1.03
Oral ulcer	- 0.368	0.454	0.417	0.692	0.28 - 1.68
ESR elevation	- 0.463	0.480	0.335	0.629	0.25 - 1.61
Signs of Nephropathy	- 0.492	0.581	0.397	0.611	0.19 - 1.91

*: Statistically significant.

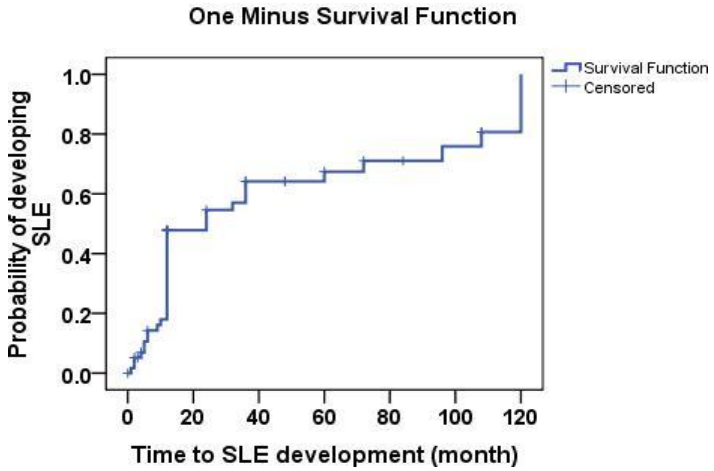

Figure 1. A Kaplan-Meier curve demonstrating duration of the disease and probability of developing to SLE among DLE patients who had SLE (n = 27).

After 2 years from the onset of the disease, 50% of patients would progress to develop SLE.

All patients were treated with topical steroids (that is, prednicarbate 0.1%, betamethasone valerate 0.1%, triamcinolone acetonide 0.02 and 0.1%, twice daily or mometasone furoate 0.1% once daily for skin lesions on face, trunk and extremities; desoximethasone 0.25%, clobetasol propionate 0.05% for scalp lesions) with favorable results. Those who had extensive lesions received intralesional corticosteroid injection (triamcinolone acetonide 10 mg/ml) and/or oral antimalarials (hydroxychloroquine 200 mg/day or chloroquine 250 mg/day) in addition to topical steroids. Oral prednisolone (0.5 - 1 mg/kg/day) was given for recalcitrant DLE cases or those with SLE who had associated major organ involvement. Table 6 summarizes the comparison of various aspects of DLE among our study and others.

DISCUSSION

Studies about the clinical course of chronic DLE were varied with respect to genetic differences, natural history and environmental triggers such as ultraviolet lights (UV),

Table 6. Comparison of various aspects of DLE among various populations.

Characteristics	Koskenmies et al. (Finnish) (n = 178)	Callen et al. (USA) (n = 62)	Jacyk et al. (Nigerian) (n = 37)	Ng et al. (Sigaporean) (n = 38)	Tang et al. (Hongkong Chinese) (n =12)	Our study (Thai) (n = 130)
Female: male ratio	3.2:1	2:1	5:1	0.7:1	1:1	5:1
Mean age at onset; years	42	39	30	38	38	36
Predilection site	N/A	Face	Face/scalp	N/A	Face/scalp	face
Photosensitivity (%)	71.3	87	N/A	N/A	58	14.6
Positive ANA (%)	28.6	21.8	2.7	23.6	67	68.5
Percentage of patients with DLE preceding SLE	N/A	6.5	2.7	N/A	17	20.7

N/A: not available.

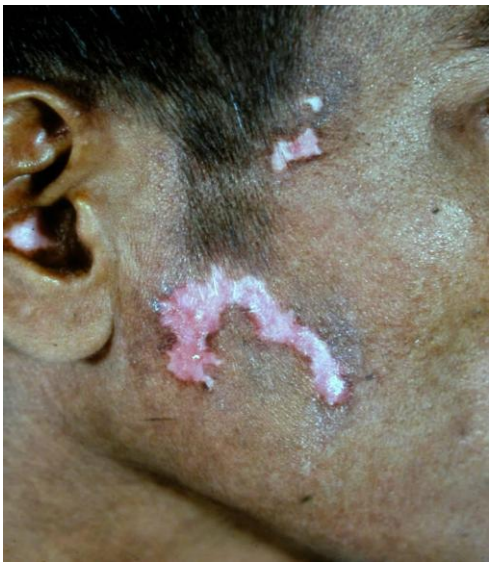

Figure 2. The photograph shows DLE lesions on the face of the patient studied.

smoking, viral infection and trauma, based on the fact that all these factors affected patient's immunological status (Greenwood, 1968; Sontheimer, 1996; Costenbader et al., 2004).

Although patients with DLE represented the vast majority of patients with CLE, the information among different race is still limited. Moreover, the spectrum of the disease ranges from benign cutaneous to those associated with severe systemic involvement. Recent studies show that, the longer the follow up period, more patients will progress to SLE (Durosaro et al., 2009).

Similar to previous studies, our study showed a female predominance with the prediction sites of face and scalp. Most of our patients began to have DLE between the second and the fourth decade which is similar to SLE, which commonly affects young adult (Jacyk and Damisah, 1979; Callen, 1982; WYM et al., 1996; Koskenmies et al., 2008).

LE-like skin lesions could be induced by UV- radiation in 40% of patients with CLE (n = 15, mostly DLE) especially UVB range (Leenutaphong and Boonchai, 1999). These might be the possible role of sunlight and effect of latitude in exacerbation of CLE. Caucasians with CLE were more susceptible to light than Asian population because their genetic contribution which determines the role of apoptotic keratinocytes via cytokines, especially tumor necrotic factors (TNF) alpha (Furukawa and Muto, 2009). Photosensitivity in Caucasian population was necessarily associated with anti-Ro antibodies but less than in non-Caucasians (Mond et al., 1989). However, phototesting in Japanese DLE patients was reported to be positive in less than 20% (Furukawa and Muto, 2009) but over 40% in Caucasian (Kuhn et al., 2001). In our study, photosensitivity was detected only in 14.6% in contrast to 71 and 87% in Finnish and American studies, respectively (Koskenmies et al., 2008; Callen, 1982). These seemed to support the result of previous studies. Moreover, UVB hardening is one of the potential therapies in patients with cutaneous LE who had photosensitivity. UVR hardening leads to improved tolerance for environmental UVR and improves activity of CLE (Sanders et al., 2006). Perhaps this postulation can explain the lower photosensitivity in Asian populations than in Caucasians.

In general, patients with DLE are reported to develop SLE in approximately 5 - 10% of cases at some point over the course of the disease. However, the studies in Caucasian population with DLE showed that the risk will even be higher (up to 20%) if the patients had generalized DLE lesions, presence of high ANA titers, signs of nephropathy and rheumatologic manifestations. These results were similar to our study of an Asian population (Tebbe et al., 1997; Werth et al., 2004; Callen, 2006).

According to previous reports, presence of ANA in DLE varied from 2 - 50%. The variety was influenced by patient selection and test sensitivity (Figure 2). Patients with DLE who had co-existent visceral involvement have a high prevalence of ANA. The speckled pattern was uncommon in patients with SLE, but it was commonly

detected in patients who had both SLE and discoid lesions (36%) and in patients with DLE (100%) (Prystowsky and Gilliam, 1977). Our study revealed that the speckled pattern was the most common pattern detected.

Some DLE patients developed SLE later in their disease course. SLE developed in 6.45% of their DLE patients within the follow up period, which ranged from one to eight years (Callen, 1982). Similarly, 6.5% of patients with DLE were reported to develop SLE later in the course (Millard and Rowell, 1979; Rowell, 1984). A recent study in a Caucasian population, 12.2% of patients with CLE (mostly DLE) had disease progression to SLE with the mean time of 8.2 years (Durosaro, 2009). As far as we know, there were no previous studies in an Asiatic population showing the association of the duration of the DLE disease and its probability of developing to SLE. Twenty percent of our DLE patients developed SLE after the disease onset. Among these patients, half of them developed SLE within 2 years. The difference in these data may be the result of ethnic, geographic and environ-mental factors. Perhaps greater availability of healthcare facilities in developed Western countries means patients in these countries are diagnosed sooner. This earlier diagnosis and management could contribute to reduce the percentage of patients who had progression of DLE to SLE, and also contribute to a longer mean duration to develop SLE.

In conclusion, our study reviewed the natural history and the clinical course of DLE in Asiatic populations, which was comparable to that of the published studies. We found not only a relatively higher percentage of positive ANA in our study than others but also a difference between our data and Caucasians in terms of lower photosensitivity but more progression of SLE in DLE patients even in those with the same risk factors. Physicians should be aware that DLE is not a static condition. Long term follow up with frequent reevaluation are necessary, especially in those who had positive ANA, abnormal urinalysis, rheumatologic symptoms and generalized DLE lesions.

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