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Study on Systemic Manifestations of Cutaneous Lupus Erythematosus with Special Reference To Renal Involvement

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Abstract

Background: This study was done to find out presence or abscence of various system involvement of body in patients with cutaneous lupus erythematosus & presence of immunological markers & pattern of positivity with special reference to spectrum renal involoement among them.

Methods:79 pts of Clinically diagnosed cases of cutaneous LE having LE specific skin lesions as classified by Gilliam's criteria & indeterminate cases diagnosis was done by histopathology of skin lesions were included in this study after considering exclusion criteria over a period of one year. Patients having condition like DM, hypertension, UTI and taking nephrotoxic drugs like acyclovir, amphotericin B, anticancer drugs like cisplatin were excluded.Detailed history,physical examinations, routine blood,urine investigations & serum C3,ANA titre-pattern,anti ds DNA,histopathology of skin lesions and kidney biopsy & histopathology of biopsy specimen were done as per proforma & data were analyzed with appropriate statistical tests to determine the significance and power of the study.

Results: The study population had male:female ratio of 4:75. Mean age of study population were 27.58. In our study among the 79 patients 32 patients(40.51%) had pure ACLE, 19 patients(24.05%) had SCLE, 15 patients(18.99%) had pure CCLE. In patients with systemic involvement, 92.41% had renal involvement, 58.9% had GI involvement, 38.36% had haematological involvement, 21.92% had serositis, 13.7% had neurological involvement and 10.96% had lymphoreticular involvement.In our study, ACLE lesions were predominant in all the system involved and highest being in patients those had neurological involvement(70%). Mean 24 hour urinary protein was much higher(1.52gm) in patients with systemic involvement than those without systemic involvement(0.84mg). Higher percentage of increased kidney echogenicity and altered CMD were found to be associated with serositis and in patients with renal involvement. Among the patients with different systemic

involvement predominant ANA titres were 1/640 followed by 1/320 & predominant pattern was homogenous followed by speckled pattern. In our study, population 89.04% patients were anti-dsDNA positive and anti-dsDNA positivity slightly higher in patients of CLE without systemic involvement(83.33%) than those with systemic involvement(82.19%).%). In patients with renal involvement 82.19% were anti-dsDNA positive.

Conclusion: This necessitates that presence of fever, psychosis, history of seizure , hepatosplenomegly, lymphadenopathy in patients presenting with cutaneous lupus erythematosus should alert the physician regarding systemic involvement. Acute, subacute, chronic cutaneous lupus erythematosus and acute and chronic cutaneous lupus erythematosus overlap, all had significant association with renal biopsy class IV. This signifies that irrespective of type of cutaneous lupus erythematosus all patients of CLE should be evaluated by renal biopsy and should not delayed till other manifestation revealed. Renal biopsy should be done in all patients of suspected SLE even anti-dsDNA is negative as our study showed, all anti-dsDNA negative patients had lupus nephritis in renal biopsy.

Keywords: ANA-Anti nuclear antibody, Anti-ds DNA antibody – Anti Double stranded DNA antibody, CLE-Cutaneous Lupus Erythematosus, ACLE-Acute Cutaneous Lupus Erythematosus, SCLE-Subacute Cutaneous Lupus Erythematosus, CCLE-Chronic Cutaneous Lupus Erythematosus,C3- complement 3,DM-Diabetes mellitus, UTI-Urinary tract infection.

Introduction

Lupus is an autoimmune disease, which affects multiple organs and system in the body.Clinical features can range from mild skin and joint involvement to severe, life-threatening internal organ disease like renal involvement. SLE evolves with time. At the start there may be one manifestation, the other organ involvement may develop with time.[1] With regards to skin there are Lupus specific skin lesions and Lupus non-specific skin lesions[2]based on biopsy. Based on Lupus specific skin lesions CLE is of three types-ACLE, SCLE and CCLE. There are localized and generalized forms of ACLE. There are two morphologic variants of SCLE: annular and papulosquamous. Chronic cutaneous lupus includes discoid LE (DLE), LE profundus (LEP), chilblain LE (CHLE), and LE tumidus (LET). LE-nonspecific lesions, on the other hand, include findings that are not characteristic of, but are frequently seen in SLE. Such lesions include Raynaud's phenomenon, periungual telangiectasias, livedo reticularis, and leukocytoclastic vasculitis.It is estimated that up to 90% of SLE patients will have pathologic evidence of renal involvement on biopsy, but only 50% will develop clinically significant nephritis. The clinical presentation of lupus nephritis is highly variable, ranging from asymptomatic hematuria and/or proteinuria to frank nephrotic syndrome to rapidly progressive glomerulonephritis with loss of renal function[3]. Various study done to find out systemic manifestation of CLE patient[4]. Studies shows 10% to 15% of SCLE patient will develop severe clinical manifestation of SLE. Most of the study done in Western countries. Very few study done over Indian population. So we aimed to study CLE patient of India, mainly Eastern India to find out various systemic involvement, specially the renal involvement. If renal involvement found then early immune suppressive therapy can be started before the clinical manifestation become evident.

Material & Methods

79 pts of Clinically diagnosed cases of cutaneous LE having LE specific skin lesions as classified by Gilliam's

criteria & indeterminate cases diagnosis was done by histopathology of skin lesions were included in this study after considering exclusion criteria over a period of one year. Patients having condition like DM, hypertension, UTI and taking nephrotoxic drugs like acyclovir, amphotericin B, anticancer drugs like cisplatin were excluded. Detailed history, physical examinations, routine blood,urine investigations & serum C3,ANA titre-pattern, anti ds DNA, histopathology of skin lesions and kidney biopsy & histopathology of biopsy specimen were done as per proforma & data were analyzed with appropriate statistical tests to determine the significance and power of the study.

Results and Analysis

We studied 79 CLE patients (satisfying the inclusion criteria) over the entire study period of 12 months. The study population had male female ratio of 4:75. Mean age of study population were 27.58 and CLE without systemic involvement and with systemic involvement were 25.33 and 27.77 respectively. The study populations 11.39% were from urban area and 88.61% were from rural area. The study population 55.70% were working at home and 44.30% were working outside home.[table1].

Table 1: Demographic Profile of Study population.

	Cutaneous Lupus without systemic involvement (n=6)	Cutaneous Lupus with systemic involvement (n=73)	Total=79	P value
Age				0.5797*
Mean±SD	25.3333 9.7502	27.7671 10.3421	27.58 10.2590	
Median, Range	23.5 14-42	25 13-61	25 13-61	
Sex (Male: Female)	1:5	3:70	4:75	0.2756**
Residence (urban: rural)	0:6	9:64	9:70	1.0000**
Occupation (Indoor: Outdoor)	4:2	40:33	44:35	0.6881**

Test for significance of difference performed by * Unpaired T-test and ** Fisher's Exact Test.

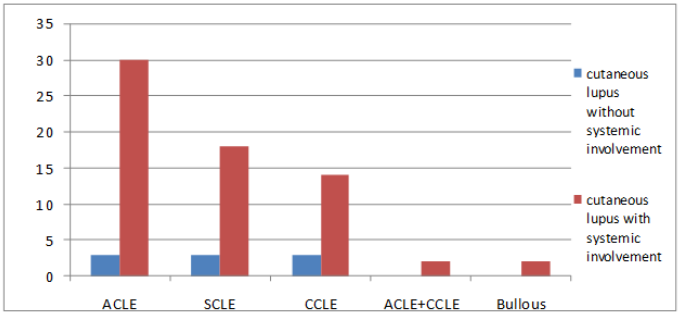
Among the 79 patients 32 patients had pure ACLE[Figure5a,5b] i.e.40.51%, 19 patients had SCLE i.e. 24.05%, 15 patients had pure CCLE i.e. 18.99%, 11 patients had both ACLE and CCLE i.e. 13.92% ,1 patient had Bullous LE i.e. 1.27% and 1patients had both ACLE and Bullous LE i.e. 1.27%[Table2,Figure1].

Table 2: Distribution of study population acc. to type of CLE

	Cutaneous Lupus without systemic involvement (n=6)	Cutaneous Lupus with systemic involvement (n=73)	Total=79	P value
Types of Cutaneous Lupus				
ACLE	2	30	32	p<0.0001*
SCLE	2	17	19	0.0098*
CCLE	2	13	15	0.0013*
ACLE+CCLE	0	11	11	
Bullous LE	0	1	1	
ACLE+ Bullous LE	0	1	1	

Test for significance of difference performed by * Unpaired T-test and ** Fisher's Exact Test

Figure1: Distribution of study population according to type of CLE. (n=79)



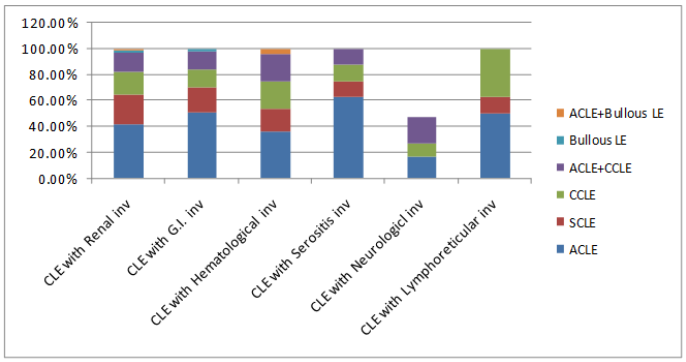
Among the 79 patients 73 patients had renal involvement i.e. 92.41%. Among 73 patients 41.1% had ACLE, 23.29% had SCLE, 17.81% had CCLE. 43 patients had GI involvements i.e. 58.9%. Among 43 patients 51.16% had ACLE, 18.60% had SCLE, 13.95% had CCLE. 28 patients had haematological involvement i.e. 38.36%. Among 28 patients 35.71% had ACLE, 17.86% had SCLE, 21.43% had CCLE.16 patients had serositis i.e. 21.92%. Among 16 patients 62.5% had ACLE, SCLE and CCLE both were 12.5%.10 patients had neurological

involvements i.e 13.7%. Among 10 patients 70% had ACLE, 10% had CCLE. 8 patients had lymphoreticular involvement i.e.10.96%. Among 8 patients 50% had ACLE, 12.5% had SCLE and 37.5% had CCLE. [Table 3,Figure2].

Table 3: Distribution of patients having different systemic involvements according to types of CLE. (n=73)

	Cutaneous Lupus with renal involvement (n=73)	Cutaneous Lupus with GI involvement (n=43)	Cutaneous Lupus with Hematological involvement (n=28)	Cutaneous Lupus with Serositis (n=16)	Cutaneous Lupus with Neurological involvement (n=10)	Cutaneous Lupus with Lymphoreticular involvement (n=8)
Types of Cutaneous Lupus						
ACLE	30	22	10	10	7	4
SCLE	17	8	5	2	0	1
CCLE	13	6	6	2	1	3
ACLE+CCLE	11	6	6	2	2	0
Bullous LE	1	1	0	0	0	0
ACLE+Bullous LE	1	0	1	0	0	0

Figure2: Distribution of patients having different systemic involvements according to types of CLE. (n=73)



Mean haemoglobin(gm%) of study population was 9.49. Mean haemoglobin of patients of CLE without systemic involvement and CLE with systemic involvement were 11.88 and 9.29 respectisely.). Mean platelet count of patients of CLE without systemic involvement and CLE with systemic involvement were 2.02 and 1.71 respectively. Mean ESR of patients of CLE without systemic involvement and CLE with systemic involvement were 31.67 and 73.12 respectively.In the study population 25.32% patients were DCT positive. No patients of CLE without systemic involvement and 27.4% CLE with systemic involvement were DCT positive. Mean reticulocyte count of patients of CLE without systemic involvement and CLE with systemic involvement were 1.38 and 1.71 respectively. Mean serum creatinine of patients of CLE without systemic involvement and CLE with systemic involvement were 0.85 and 0.95 respectively.Mean serum albumin of patients of CLE without systemic involvement and CLE with systemic involvement were 3.82 and 2.96 respectively.[Table4]

	Cutaneous Lupus without systemic involvement (n=6)	Cutaneous Lupus with systemic involvement (n=73)	Total=79	P value
Haemoglobin				
Mean SD	11.8833 2.2284	9.2918 2.3577	9.4886 2.4345	0.981*
Total count				
Mean SD	6.2083 1.7551	6.9160 3.4952	6.8623 3.3926	0.125*
Platelet count				
Mean SD	2.0150 0.1715	1.7088 0.8861	1.7320 0.8564	0.002*
ESR				
Mean SD	31.6667 16.3544	73.1370 31.1628	69.9873 32.1840	0.150*
DCT(Positive:Negetive)	0:6	20:53	20:59	0.3287**
Reticulocyte count				
Mean SD	1.3833 0.8727	1.7110 1.0969	1.6861 1.0803	0.650*
Serum creatinine				
Mean SD	0.8500 0.2429	0.9460 0.4998	0.9387 0.4848	0.109*
Serum albumin				
Mean SD	3.8167 0.8658	2.9589 0.7615	3.0241 0.7973	0.553*

Test for significance of difference performed by * Unpaired T-test and ** Fisher's Exact Test

Pus cell in urine present 31.65% of study population. 16.67% patients of CLE without systemic involvement and 32.88% CLE with systemic involvement had pus cell in urine. Among the patients with CLE without systemic involvement 33.33% had no proteinuria, 50% had 1+ proteinuria and on 16.67% had 2+ proteinuria and among the patients of CLE with systemic involvement 10.96% had no proteinuria, 35.62% had 1+ proteinuria, 26.03% had 2+ proteinuria, 21.92% had 3+ proteinuria, 5.48% had 4+ proteinuria. . Among the patients with CLE without systemic involvement no patients had RBC cast in urine and among the patients of CLE with systemic involvement 61.64% had no RBC cast in urine, 28.77% had 1+ RBC cast in urine, 8.22% had 2+ RBC cast in urine, 1.37% had

3+ RBC cast in urine. Among the patients with CLE without systemic involvement no patients had granular involvement 47.95% had no granular cast in urine, 32.88% had 1+ granular cast in urine, 16.44% had 2+ granular cast in urine, 2.74% had 3+ granular cast in urine.Mean 24 hour urinary protein of patients of CLE without systemic involvement and CLE with systemic involvement were 0.84mg and 1.52gm respectively.[Table5]

cast in urine and among the patients of CLE with systemic

Table 5: Urinary finding of Study Population.

	Cutaneous Lupus without systemic involvement (n=6)	Cutaneous Lupus with systemic involvement (n=73)	Total=79	P value
Pyuria (Present: Absent)	1:5	24:49	25:54	0.6588**
Urine albumin				0.3618*
0	2	8	10	
1+	3	26	29	
2+	1	19	20	
3+	0	16	16	
4+	0	4	4	
Urine RBC				0.1464*
0	5	24	29	
1+	0	28	28	
2+	1	13	14	
3+	0	7	7	
4+	0	1	1	
Urine RBC CAST				0.3124*
0	6	45	51	
1+	0	21	21	
2+	0	6	6	
3+	0	1	1	
Urine Granular cast				0.1107*

0	6	35	41	
1+	0	24	24	
2+	0	12	12	
3+	0	2	2	
24 Urinary Protein				
Mean SD	0.8390 2.0014	1.5165 1.5108	1.4651 1.5480	0.266*

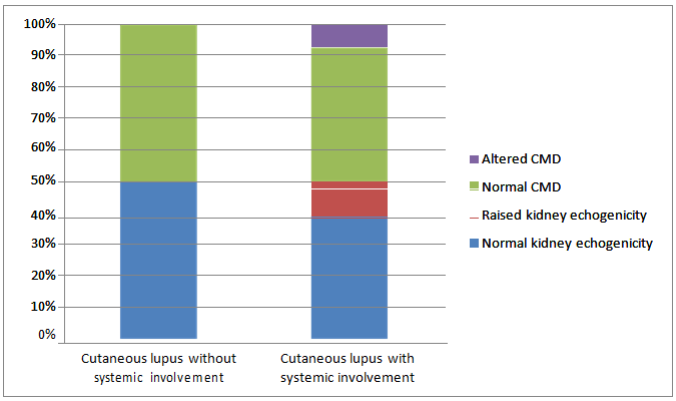
Test for significance of difference performed by * Unpaired T test and ** Fisher's Exact Test

In USG kidney echogenicity raised 20.25% of study population and CMD altered 13.92% of study population. Kidney echogenicity and CMD both were normal in patients of CLE without systemic involvement and CLE with systemic involvement raised kidney echogenicity and altered CMD were found 21.92% and 15.07% patients respectively[Table5a]. In patients with renal involvement raised kidney echogenicity were found 21.92%.[Table6,figure3].Table 6: USG kidney findings of Study Population.

	Cutaneous Lupus without systemic involvement (n=6)	Cutaneous Lupus with systemic involvement (n=73)	Total=79	P value
Echogenicity (Normal:Raised)	6:0	57:16	63:16	0.3383**
CMD(Normal:Altered)	6:0	62:11	68:11	0.5875**

Test for significance of difference performed by ** Fisher's Exact Test

Figure3: Distribution of kidney Echogenicity and CMD in the study population. (n=79).



Mean serum C3 (mg/dl) of study population was 61.56. Mean serum C3 of patients of CLE without systemic involvement and CLE with systemic involvement were 111.67 and 57.44 respectively [Table7]. In our study, mean serum C3 was 61.56 30.96 and much lower mean serum C3 was found among systemic invloved pt.. So low serum C3 is a strong predictor systemic involvement.

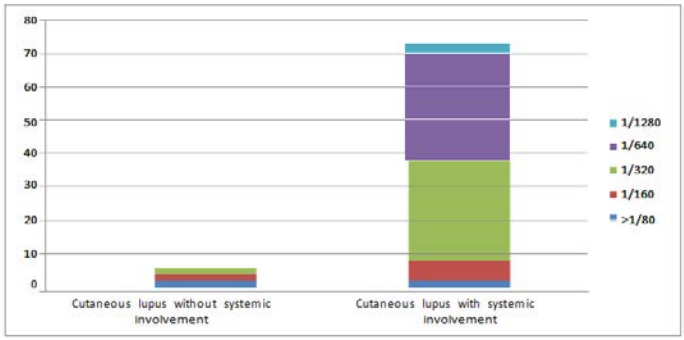
Table 7.Immunological investigation of study population.

	Cutaneous Lupus without systemic involvement (n=6)	Cutaneous Lupus with systemic involvement (n=73)	Total=79	P value
Serum C3				
Mean SD	111.6667 29.2971	57.4425 27.4285	61.5608 30.9591	0.694*
ANA Titre				0.0022*
>1/80	2	2	4	
1/160	2	6	8	
1/320	2	30	32	
1/640	0	33	33	
1/1280	0	2	2	
ANA Pattern				0.7801*
Homogenous	3	40	43	
Speckled	3	29	32	
Homogenous +Speckled	0	4	4	
Anti Ds DNA(Positive:Negetive)	5:1	60:13	65:14	1.0000**

Test for significance of difference performed by * Unpaired T-test and ** Fisher's Exact Te

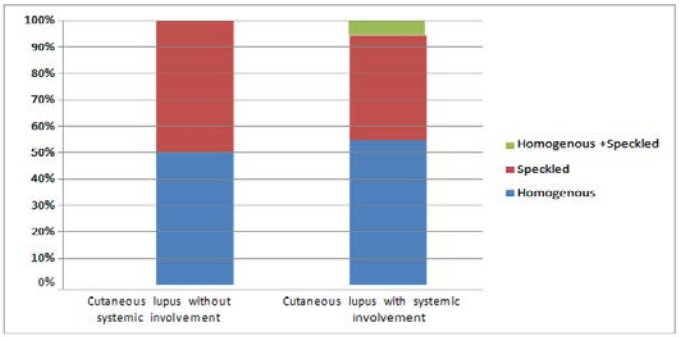
ANA titre of patients of CLE without systemic involvement were 33.33% had >1/80, 33.33% had 1/160 and 33.33% had 1/320.ANA titre of patients CLE with systemic involvement were 2.74% had >1/80, 8.22% had 1/160, 41.1% had 1/320, 45.21% had 1/640 and 2.74% had 1/1280[Table7,Figure4].ANA titre of patients with renal involvement were 2.74% had >1/80, 8.22% had 1/160, 41.1% had 1/320, 45.21% had 1/640 and 2.74% had 1/1280.Vitali C and colleagues showed in their study, virtually all the patients (98%) were antinuclear antibody positive[4]. F J Tapanes and colleagues established the fact that absence of ENA antibodies increased eleven-fold the odds ratio to develop SLE nephropathy. They suggested that the ENA negative cluster may predict development of the most severe forms of renal lupus[22]. Cairns et al. Reported 11 ANA-negative patients whose onset of SLE began with clinical glomerulonephritis as the initial manifestation[23].In our study, in patients of CLE without systemic involvement three type of ANA titre were present-1/320, 1/160 and >1/80 and each were 33.33% but in patients with systemic involvement predominant titre were 1/640(45.21%) followed by 1/320(41.1%), 1/160(8.22%), 1/1280 and >1/80 both were 2.74%.. So ANA titre 1/640 and 1/320 is strong predictor of systemic involvement.

Figure4: Distribution of ANA titre in the study population. (n=79)



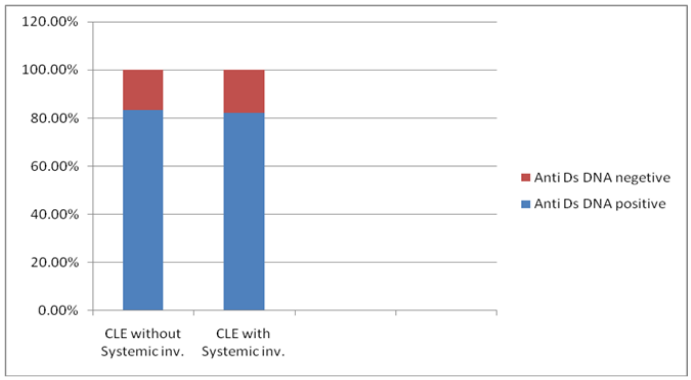
ANA pattern of the study population were 54.43% had homogenous, 40.51% had speckled and 5.06% had both homogenous and speckled pattern. ANA pattern of patients of CLE without systemic involvement were 50% had homogenous and 50% had speckled pattern.ANA pattern of patients CLE with systemic involvement were 54.79% had homogenous, 39.73% had speckled and 5.48% had both homogenous and speckled pattern[Table6a,Figure40a].In patients with renal involvement ANA pattern were 54.79% had homogenous, 39.73% had speckled and 5.48% had both homogenous and speckled pattern.[Figure5].

Figure5: Distribution of ANA pattern in study population. (n=79)



AntiDsDNA was positive in 89.04% of study population. Among the patients of CLE without systemic involvement and CLE with systemic involvement were 83.33% and 82.19% were anti Ds DNA positive respectively[Table7,Figure6]

Figure 6: Distribution of Anti Ds DNA in study population. (n=79)

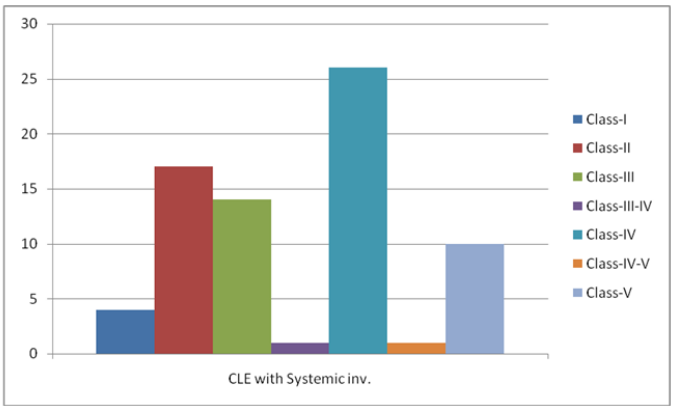


Among 79 patients kidney biopsy done only in 73 patients, those had systemic manifestation. Renal biopsy class among the patients of CLE with systemic manifestation were 5.48% had class I, 23.29% had class II, 19.18% had class III, 35.62% had class IV, 13.7% had class V lupus nephritis and 1.37% had class III-IV overlap and 1.37% had class IV-V overlap[Table8,Figure7].

Table8. Renal biopsy findings of patients of CLE with systemic manifestations.

	Cutaneous Lupus with systemic involvement (n=73)	Total=73
Class		
I	4	4
II	17	17
III	14	14
III-IV	1	1
IV	26	26
IV-V	1	1
V	10	10

Figure7: Distribution of renal biopsy class in patients of CLE with systemic involvement (n=73)



In our study, kidney biopsy were done in 73 patients and predominant biopsy class was class IV. In our study, significant association was found between renal biopsy

class IV and ACLE(p=0.003), SCLE(p=0.011), CCLE(p=0.002) and ACLE CCLE overlap(p=0.020). This signifie that irrespective of type of CLE all patients of CLE should be evaluated by renal biopsy and should not delayed till other manifestation revealed.

Discussion

In our study, among the patients of CLE without systemic involvement 83.33% were female and among the patients of CLE with systemic involvement 95.89% were female. Vitali C and colleagues in their study using a detailed questionnaire, the cumulative historical and current demographic, clinical and serological data on 704 SLE patients from 29 European centers and 14 countries showed that Ninety-three percent of the patients were Caucasian and the female/male ratio was 10:1[1]. Among the demographic parameters our study differed from the western literature only in age at presentation. Our patients were younger(27.58±10.26 yrs) than patients evaluated in other studies by Vitali C et al, Bastian H M et al and Samanta A et al[4,5,6] .In our study among the 79 patients 32 patients(40.51%) had pure ACLE, 19 patients(24.05%) had SCLE, 15 patients(18.99%) had pure CCLE, 11 patients(13.92%) had both ACLE and CCLE,1 patient(1.27%) had Bullous LE and 1 patients(1.27%) had ACLE and Bullous LE overlap. No such studies have been made for CLE but DLE is considered more common among African Americans and SCLE is more common among Caucasians. DLE is the mostcommon subset (80%), followed by SCLE (15%) and less than 5% are other more rare types of CLE such as lupus profundus or lupus panniculitis.[7]In patients with systemic involvement, 92.41% had renal involvement, 58.9% had GI involvement, 38.36% had haematological involvement, 21.92% had serositis, 13.7% had neurological involvement and 10.96% had lymphoreticular involvement.In our study, ACLE lesions were predominant in all the system involved and highest being in patients those had neurological involvement(70%). Mean haemoglobin of patients of CLE with systemic involvement were much lower(9.29 2.36) than the patients of CLE without systemic involvement(11.88 2.23). Michael et al. reported that 87 of 111 patients with SLE (78%) had a hemoglobin level of lower than 12 gm/dL at diagnosis[8]ESR may be looked upon as an inflammatory marker in SLE. In Batimore Pediatric nephrology(3rd Ed) staging of SLE needs ESR>25 mm/hr as an important component. Mean ESR of patients of CLE with systemic involvement was higher (73.12 31.16) than the patients of CLE without systemic involvement(31.67 16.35). In our study, significant positive association was found between ESR and urine RBC(p=0.007).This correlation can be explain as a component of LE flare. Lower mean serum albumin was found in patients of CLE with systemic involvement(2.96 0.76) than the patients of CLE without systemic involvement(3.82 0.87).In our study, Proteinuria was also found in 66.67% patients of without any systemic involvement. So proteinuria does not always indicate systemic involvement. Mean 24 hour urinary protein much higher(1.52) in patients with systemic involvement than those without systemic involvement(0.84). So higher 24 hour urinary protein is strong predictor of systemic involvement and chance of serositis much higher along with renal involvementHigher percentage of increased kidney echogenicity and altered CMD were found to be associated with serositis and in patients with renal involvement.It has been found that pt with systemic involvement had much lower C3 level,So low serum C3 is a strong predictor systemic involvementIn our study, anti nuclear antibody(ANA) titre and pattern was studied by indirect immune fluorescent

test using Hep-2 cell lines. Another serological marker considered was anti dsDNA. Vitali C and colleagues showed in their study, virtually all the patients (98%) were antinuclear antibody positive[4]. F J Tapanes and colleagues established the fact that absence of ENA antibodies increased eleven-fold the odds ratio to develop SLE nephropathy. They suggested that the ENA negative cluster may predict development of the most severe forms of renal lupus[9]. Cairns et al. Reported 11 ANA-negative patients whose onset of SLE began with clinical glomerulonephritis as the initial manifestation[10].Among the patients with different systemic involvement predominant titres are 1/640 followed by 1/320. . So ANA titre 1/640 and 1/320 is strong predictor of systemic involvement.In our study,Among the patients with different systemic involvement predominant pattern was homogenous followed by speckled pattern.In our study, population 89.04% patients was anti-dsDNA positive and anti-dsDNA positivity slightly higher in patients of CLE without systemic involvement(83.33%) than those with systemic involvement(82.19%).%). In patients with renal involvement 82.19% was anti-dsDNA positive. So anti-dsDNA positivity is strong predictor of systemic involvement. Vitali C and colleagues in their study found anti-ds-DNA antibodies (76%),as a frequent serological abnormality[4]. In our study, anti-dsDNA was significantly associated renal biopsy class with p value 0.013 but it also noted that 14 patients were anti-dsDNA negative and among them renal biopsy was done in 13 patients. Out of 13 patients 3 patients had class I, 4 patients had class II, 2 patients had class III, 3 patients had class IV and 1 Patients had class V lupus nephritis. This signifies that renal biopsy should be done, even anti-dsDNA is negative in suspected SLE patients.

Conclusion

This necessitates that presence of fever, psychosis, history of seizure , hepatosplenomegly, lymphadenopathy in patients presenting with cutaneous lupus erythematosus should alert the physician regarding systemic involvement. Acute, subacute, chronic cutaneous lupus erythematosus and acute and chronic cutaneous lupus erythematosus overlap, all had significant association with renal biopsy class IV. This signifies that irrespective of type of cutaneous lupus erythematosus all patients of CLE should be evaluated by renal biopsy and should not delayed till other manifestation revealed. Renal biopsy should be done in all patients of suspected SLE even anti-dsDNA is negative as our study showed, all anti-dsDNA negative patients had lupus nephritis in renal biopsy.

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