Original Research Paper

Volume - 10 | Issue - 8 | August - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Rheumatology

ASSOCIATION BETWEEN MUCOCUTANEOUS MANIFESTATIONS AND SYSTEMIC INVOLVEMENT IN CHILDHOOD ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT **Background:** Certain mucocutaneous manifestations are associated with specific systemic involvement in systemic lupus erythematosus(SLE). Evidence about the same from India in childhood onset SLE(cSLE) is limited.

Objective: To study the association of mucocutaneous manifestations with systemic involvement in cSLE.

Method: This was a retrospective case control study. The patients consulted the pediatric rheumatology department between January 2012 and December 2018. Patients were diagnosed with cSLE by an experienced pediatric rheumatologist. The clinical manifestations at presentation were recorded and the association studied.

Results: Out of 107 patients included in the study, 21 patients had no mucocutaneous manifestations at presentation. Hematological involvement was the most common systemic involvement. Mucosal ulcer was the most common mucocutaneous manifestation. Malar rash was associated with systemic involvement in males.

Conclusion: cSLE without mucocutaneous manifestations can have severe disease at presentation. Malar rash was associated with systemic involvement in males.

KEYWORDS : Childhood onset SLE, mucocutaneous, systemic, manifestations

INTRODUCTION

Childhood onset systemic lupus erythematosus (cSLE) is an autoimmune and autoinflammatory multisystem disease with heterogeneous presentation [1,2]. The symptoms, signs and laboratory manifestations can occur either simultaneously or sequentially in cSLE. In some cases, mucocutaneous (mc) manifestations develop first followed by systemic manifestations; in some, they develop simultaneously. It is possible for the phenotype to remain as mc manifestations only without any systemic manifestations or there could be only systemic manifestations without any mc manifestations at all. Studies have shown that cSLE can have severe disease with greater activity and abrupt onset as compared to adult onset SLE [1,2]. In the case of cSLE it is prudent to perform accurate and prompt diagnosis as the clinical presentation can vary from acute disease, rapidly fatal disease to a chronic disease with intermittent or continuous course[3].

Lack of awareness of the disease itself, with its common and rare presentations among the primary care physicians results in significant delay in diagnosis and consequently serious complications to the patient. It was clearly demonstrated previously that the identification of signs and symptoms at disease presentation was the relevant factor influencing early referral in child hood onset rheumatic diseases[4]. Mc manifestations help in diagnosis[5]. While a typical malar rash or extensive skin vasculitis, both of which are included in the criteria for SLE diagnosis, may trigger consideration of SLE as a diagnosis and prompt the physician for work up, a lack of mc manifestations can cause a delay in the same. Mc manifestations were also attempted to use as predictors of prognosis[6]. Previous studies in adult onset SLE (aSLE) have shown that some typical mc manifestations can predict the future development of systemic manifestations[7] and also it can act as indicator of disease activity[8]. In the case of cSLE also similar reports are available[9].

It was in this background that the current study was done. The objective of the current study was to describe the clinical parameters of cSLE at presentation and to look for the association of mc manifestations with systemic involvement.

MATERIALS AND METHODS

This was a retrospective case control study. The electronic medical records of all the cSLE patients who attended the pediatric rheumatology OPD and diagnosed by an experienced pediatric rheumatologist, between 2012 January and 2018 December were reviewed. The parameters recorded were age, sex, mc and systemic manifestations during presentation and lab parameters which aided in the diagnosis of systemic involvement. “Criteria mc manifestations” were defined as those mc manifestations included in ACR 1997 and SLICC 2012 criteria (malar rash, photosensitivity, oral/mucosal ulcers, non scarring alopecia, Acute cutaneous lupus erythematosus(ACLE) which include malar rash, bullous lesions, toxic epidermal necrolysis, maculopapular lupus rash, Subacute cutaneous lupus erythematosus(SACLE) that include nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, chronic cutaneous lupus erythematosus(CCLE) which include classical discoid rash-localized (above the neck) and generalized -above and below the neck, hypertrophic (verrucous) lupus, lupus panniculitis (profundus); “non-criteria mc manifestations” included Raynauds phenomenon, urticaria and gangrene. “Any systemic involvement” was defined as any of renal, neurologic, cardiac or hematologic involvement (leucopenia/ lymphopenia/ thrombocytopenia/ autoimmune hemolytic anemia(AIHA). “Any severe systemic involvement” is defined as any of renal, neurologic, cardiac, thrombocytopenia or AIHA. Frequency of initial presentation with fever, arthritis and macrophage activation syndrome(MAS) were also recorded.

Statistical analysis was performed using IBM SPSS 20.0. Categorical variables were expressed using frequency and percentage. Continuous variables were presented by mean and standard deviation. To test the statistical significance of the association between categorical variables (mc manifestations) and outcome(systemic involvement) Chi square test was used.

RESULTS

A total of 107 paients were included in the study. Female:male ratio was 4.35:1(87:20), mean age was 12.5±3 yrs. The clinical

manifestations and frequency were given in figure 1a. 21 patients were not having any mc manifestations, 86 patients were having some kind of mc manifestation and 89 patients were having some systemic involvement. The systemic involvement in cSLE with and without mc manifestations was given in figure 1b.

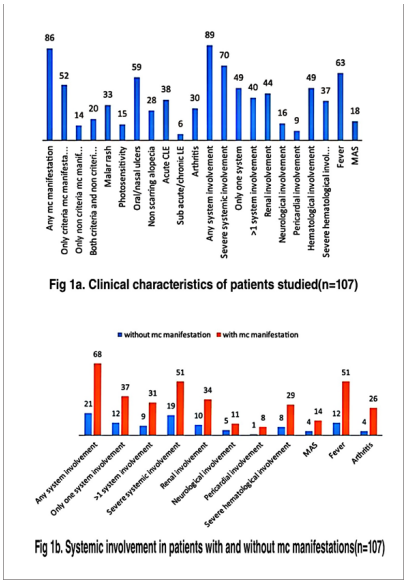

Fig 1a. Clinical characteristics of patients studied(n=107)

Fig 1b. Systemic involvement in patients with and without mc manifestations(n=107)

Figure 1: Clinical manifestations in cSLE (n=107)

Foot note:mc- mucocutaneous, MAS- macrophage activation syndrome

The association between mc manifestations and systemic involvement are given in table 1.

Table 1: Association Between Mc Manifestations And Systemic Involvement (n=107)

Parameter	Category	Mc positive (n=86)	Mc negative (n=21)	p value
Age at diagnosis		12±3.15	13±2.33	
Female/Male		71/15	16/5	
Any systemic involvement	Yes No	68(79.1) 18(20.9)	21(100) 0(0)	0.021
Any severe systemic involvement	Yes No	51(59.3) 35(40.7)	19(90.5) 2(9.5)	0.009
Only one system involvement	Yes No	37(43) 49(57)	12(57.1) 9(42.9)	0.329
>one system involvement	Yes No	31(36) 55(64)	9(42.9) 12(57.1)	0.619
Renal involvement	Yes No	34(39.5) 52(60.5)	10(47.6) 11(52.4)	0.622
Neurological involvement	Yes No	11(12.8) 75(87.2)	5(23.8) 16(76.2)	0.302
Pericardial involvement	Yes No	8(9.3) 78(90.7)	1(4.8) 20(95.2)	0.685
Severe Hematological involvement	Yes No	29(33.7) 57(66.3)	8(38.1) 13(61.9)	0.799
MAS	Yes No	14(16.3) 72(83.7)	4(19) 17(81)	0.75

Foot note:mc-mucocutaneous, MAS- macrophage activation syndrome

The association of specific mc manifestations is given in table 2.

Table 2: Association In Patients With Mc Manifestations (n=86)

Parameter	Category	Systemic involvement, n(%)	No systemic involvement, n(%)	p value
Criteria mc manifestation	Yes(52) No (34)	41(78.8) 27(79.4)	11(21.2) 7(20.6)	1
Non-criteria mc manifestation	Yes(14) No (72)	9(64.3) 59(81.9)	5(35.7) 13(18.1)	0.158
Both criteria and non criteria mc manifestation	Yes(20) No(66)	18(90) 50(75.8)	2(10) 16(24.2)	0.221
Malar rash	Yes(33) No(53)	30(90.9) 38(71.7)	3(9.1) 15(28.3)	0.054
Photosensitivity	Yes(15) No(71)	13(86.7) 55(77.5)	2(13.3) 16(22.5)	0.727
Acute CLE	Yes(38) No(48)	34(89.5) 34(70.8)	4(10.5) 14(29.2)	0.06
Sub acute/chronic LE	Yes(6) No(80)	5(83.3) 63(78.8)	1(16.7) 17(21.3)	1
Oral/nasal ulcers	Yes(59) No(27)	48(81.4) 20(74.1)	11(18.6) 7(25.9)	0.569
Non scarring alopecia	Yes(28) No(58)	21(75) 47(81)	7(25) 11(19)	0.577
Association of malar rash with systemic involvement wrt gender				
Malar rash in males	Yes(9) No(6)	9(100) 3(50)	0(0) 3(50)	0.044
Malar rash in females	Yes(24) No(47)	21(87.5) 35(74.5)	3(12.5) 12(25.5)	0.238

Foot note: mc- mucocutaneous, CLE-cutaneous lupus erythematosus, LE- lupus erythematosus, wrt- with respect to

DISCUSSION

The main aim of our study was to see if there is any association between mc manifestation and systemic involvement in cSLE based on clinical features at presentation.

In our study, there were 107 patients with female:male ratio 4.35:1 and the mean age was 12.5±3 years(range 5-17 years). Many publications which studied the clinical features of cSLE were available; three of them were compared with the current study in table 3.

Table 3: Comparison of different studies.

Parameter	Andy S.K et al[10]	Hiraki L.T et al[11]	Ilias M.I et al[12]	Current study
Mean age at presentation (years)	9.5	13	12	12.4
Age of population studied (years)	<12	<18	<18	<18
Female:Male	2.6:1	4.5:1	10:1	4.35:1
Mean follow up (years)	1	3.5	4	3.5
Malar rash (%)	72	61	25	31
Photosensitivity (%)	52	17	20	14
DLE/SCLE (%)	4	38	18	6
Oral/Nasal ulcer (%)	32	21	40	55
Non scarring alopecia (%)	26	22	24	26
Renal involvement (%)	40	37	60	41
Nervous system involvement (%)	26	16	9	15
Cardiac involvement (%)	8	NA	NA	8
Hematologic involvement (%)	56	55	60	46
Arthritis (%)	60	61	44	28
ANA (%)	92	100	98	100
Fever (%)	94	NA	NA	59

Foot note: DLE-Discoid lupus Erythematosus, SCLE-sub acute cutaneous lupus erythematosus, ANA-Anti Nuclear Antibody, NA-Not available

In our study the most common clinical manifestation at presentation was “any system involvement” (83.2%) followed by “any mc manifestation” (80.4%). This may be because, ours was a tertiary care centre and more patients with systemic involvement would be referred to us; and more patients with mc manifestations would have been diagnosed at the periphery or by dermatologists. Out of 107 patients, the duration of symptoms was available only for 83 patients only from the records. 67 out 86 patients with mc manifestation had a mean duration of symptoms before diagnosis of 0.36±0.43 years and 16 out

of 21 patients without mc manifestations had a mean duration of symptoms before diagnosis of 0.48±0.8 years. The duration of symptoms before diagnosis was lesser for patients with mc manifestations, the difference was not significant (p value 0.96).

Fever was present in 58.9% of the patients. Among the systemic involvement, hematological involvement was the most common (49%) followed by renal involvement (41.1%). Out of dermatologic involvement, oral/nasal ulcer was the most common (55.1%) followed by ACLE(38%). In the study by Kandy et al, Hiraki et al and Ilias et al most common dermatological manifestation was malar rash and oral/nasal ulcer and the most common system involved was hematologic. While the frequency of arthritis was lower in our cohort, frequency of non scarring alopecia and renal involvement was similar as compared to others [10,11,12].

As described by Lopes et al, our cohort had patients with multisystem involvement at presentation (40/107)[3].

Previous studies have mentioned the association between mucocutaneous manifestations and systemic involvement in cSLE and adult onset SLE (aSLE)[7,8,9]. In our study, we found that out of 107 cSLE patients, 21 patients had no mc manifestations and all of them had some systemic involvement, with 19 of them having severe systemic involvement. These patients were evaluated for SLE as they had multisystem involvement or abnormal renal function including abnormal urine routine tests or prolonged fever of unknown etiology or prolonged hematological abnormalities of unknown etiology at presentation.

We studied the mc manifestations as "criteria mc manifestations" and "non-criteria mc manifestations" instead of specific and non specific manifestations as the general practitioners are more aware of criteria manifestations. Also classification into lupus specific and lupus non-specific mc manifestations require histopathological examination to be done.

In our cohort, none of the criteria and non criteria mc manifestations were associated with MAS (p value >0.05).

When the patients with only mc manifestations were analysed, none of the mc manifestations were significantly associated with systemic involvement though malar rash and ACLE showed border line association (p value 0.06 and 0.054 respectively). Gender wise evaluation showed that in male children, malar rash was significantly associated with systemic involvement (p value 0.044). None of the mc manifestation was found to be associated with any specific systemic involvement.

Previous studies in aSLE have shown that vasculitic skin lesions were associated with neuropsychiatric lupus [13], bullous skin lesions were associated with systemic flares[8,14], specifically renal flare[15]. Generalized maculopapular lesions, and non-scarring alopecia were associated with more active disease [8]. Nonscaring alopecia, photosensitivity, oral ulcers, and malar rash were associated with systemic involvement [7]. In an abstract, Fonseca et al have reported that frequency of renal and hematological involvement was more in jSLE patients with mc involvement [16].

The current study attempted to look for association between mc manifestations and systemic involvement in cSLE at presentation. Since it was a retrospective study from a single centre, it has the weakness of small sample size and the information was incomplete for duration of symptoms. Gastrointestinal system and respiratory system involvement were not studied; also the antibody profile. Clinical manifestations which evolved after presentation were not studied.

CONCLUSION

cSLE can present with serious systemic involvement as initial manifestation. Whenever a child is presenting with pyrexia of unknown origin, multisystem involvement, hematological abnormalities or abnormal urine examination report, cSLE should also be considered in the differential diagnosis. Malar rash was found to be associated with systemic involvement in male cSLE. Further prospective large scale studies in cSLE should be undertaken to know the association of mc manifestations with systemic involvement , disease activity and autoantibody profile.

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