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Impact of Autoimmune Cytopenias on Severity of Childhood-onset Systemic Lupus Erythematosus: A Single-Center Retrospective Cohort Study

Ekemini A. Ogbu, MD MSc[1], **Shanmuganathan Chandrakasan, MD**[2], **Kelly Rouster-Stevens, MD MS**[3], **Larry A. Greenbaum, MD PhD**[4], **Ignacio Sanz, MD**[5], **Scott E. Gillespie, MS MSPH**[6], **Chelsea Marion, MD**[7], **Karli Okeson, DO**[6], **Sampath Prahalad, MD MSc**[3]

[1]Department of Pediatrics, Division of Pediatric Allergy, Immunology and Rheumatology, Johns Hopkins University, Maryland, USA

[2]Department of Pediatrics, Division of Pediatric Hematology/Oncology, Emory University School of Medicine and Children's Healthcare of Atlanta, Georgia, USA

[3]Department of Pediatrics, Division of Pediatric Rheumatology, Emory University School of Medicine and Children's Healthcare of Atlanta, Georgia, USA

[4]Department of Pediatrics, Division of Pediatric Nephrology, Emory University School of Medicine and Children's Healthcare of Atlanta, Georgia, USA

[5]Department of Medicine, Division of Rheumatology, Emory University School of Medicine

[6]Department of Pediatrics, Emory University School of Medicine, Georgia, USA

[7]Children's Healthcare of Atlanta, Georgia, USA

Abstract

Objective: To assess whether children with autoimmune cytopenias prior to or at diagnosis of systemic lupus erythematosus (cSLE), differ phenotypically from other cSLE patients; and have a lower risk and severity of lupus nephritis (LN) as observed in prior adult studies. To assess the effect of prior immune therapy for autoimmune cytopenias on 2-year risk of LN.

Methods: This was a retrospective cohort study of incident cSLE cases. We included patients aged less than 17 years at diagnosis. We excluded patients with LN at cSLE diagnosis. Our follow-up period was 2 years. We defined autoimmune cytopenias as either autoimmune hemolytic anemia, immune thrombocytopenia or Evan's syndrome.

Results: Forty-three (33%) of the 130 patients had autoimmune cytopenias before or at cSLE diagnosis. Those with autoimmune cytopenias had significantly more neuropsychiatric symptoms and higher mean ESR but less arthritis, malar rash and myositis versus those without autoimmune cytopenias. They had lower 2-year incidence proportion of LN compared to other cSLE patients

Correspondence to: Dr. Ekemini Ogbu, Johns Hopkins University, 600 N Wolfe Street, CMSC 1102, Baltimore, Maryland 21287. eogbu1@jhmi.edu Phone: 410 955 5883 Fax: 410 955 0229.

Conflicts of interest: None

DATA ACCESSIBILTY STATEMENT

The data analyzed for this study is available from the corresponding author on reasonable request.

(7% vs 15%). Of the 16 patients who developed LN, those with autoimmune cytopenias had mostly class V (2 of 3 patients) versus mostly class III and IV in those without autoimmune cytopenias (6 of 12 patients). None of the 13 patients pre-treated for autoimmune cytopenias developed LN.

Conclusion: Patients with autoimmune cytopenias before or at cSLE diagnosis have intriguing differences from other cSLE patients. They may represent a unique sub-type of cSLE patients and should be further explored.

Keywords

Systemic Lupus Erythematosus; Pediatrics; Nephritis; Anemia; Thrombocytopenia

INTRODUCTION

Autoimmune cytopenias including autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP) and Evans syndrome (ES) may precede or be present at the time of diagnosis of childhood-onset systemic lupus erythematosus (cSLE) [1–4]. Surprisingly, studies suggest that adult patients with SLE and coexisting autoimmune cytopenias have lower rates of lupus nephritis (LN) compared to those patients without autoimmune cytopenias and may therefore represent a unique sub-population [5–7]. This observation is unexplained and has not been well-studied in children.

Some patients with idiopathic autoimmune cytopenia, undergo immunosuppressive or immunomodulatory therapy similar to cSLE treatment. Mouse models suggest that early immune modifying therapy can impact SLE phenotype by preventing development of endothelial dysfunction and reducing progression of nephritis [8, 9]. Despite advances in therapeutics, outcomes for LN, especially in cSLE, are still sub-optimal [2, 10, 11]. It is unclear if coexisting autoimmune cytopenia is associated with a better clinical outcome in cSLE [12–16].

We conducted a retrospective cohort study comparing cSLE patients with preceding or co-existing autoimmune cytopenias at diagnosis to other cSLE patients. We hypothesized that patients with autoimmune cytopenias will have decreased 2-year risk and severity of LN compared to those without autoimmune cytopenia. We further hypothesized that receiving treatment for autoimmune cytopenia prior to cSLE diagnosis will decrease the 2-year risk of LN. Finally, as our study was conducted on one of the largest single-center cohorts of diverse cSLE patients in the United States, we performed a descriptive analysis of our population of pediatric patients without LN at cSLE diagnosis and assessed whether patient characteristics at diagnosis were associated with the 2-year risk of LN.

MATERIALS AND METHODS

Study design and setting

This was a retrospective cohort study of incident cSLE patients at the Emory Children's Center/ Children's Healthcare of Atlanta pediatric rheumatology service over a 16-year

period. Approval of the study protocol with waiver of informed consent was obtained from the Children's Healthcare of Atlanta Institutional Review Board (#16–114).

Characteristics of Study Population

We extracted patient data from electronic medical records and paper charts with ICD-9 or 10 codes corresponding to a diagnosis of SLE between January 1, 2000 and June 30, 2016. We included patients who were diagnosed at age less than 17 years and who met at least 4 of the 11 American College of Rheumatology (ACR) and/or at least 4 of the 17 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE. For the SLICC criteria, this included at least 1 clinical and 1 immunologic criteria [17, 18]. We excluded patients with a pre-existing diagnosis of cSLE who transferred care to our center and those with LN at time of cSLE diagnosis. Our follow-up period was 2 years from time of cSLE diagnosis.

Measurements

We defined time of cSLE diagnosis (baseline) as time of initial evaluation for cSLE by a pediatric rheumatologist at our institution. Variables defined at diagnosis included data at initial evaluation up to 1-month post cSLE diagnosis. Autoimmune cytopenia referred to AIHA, thrombocytopenia and/or ES. We defined the presence of autoimmune cytopenia as a preceding diagnosis of a primary autoimmune cytopenia and/or the presence of an autoimmune cytopenia at cSLE diagnosis and up to 1-month post cSLE diagnosis. We defined AIHA as hemoglobin ≤10 g/dl and positive direct Coombs. We defined ITP as thrombocytopenia <100,000/mm^3 and ES as concurrent or sequential AIHA and ITP.

Demographic, clinical and laboratory data were obtained at baseline. We used age greater than 9 years as a proxy for puberty for both males and females. We defined positive ANA as titers ≥ 1:40 [17, 18]. We included the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) as a measure of overall cSLE activity [19]. Neuropsychiatric symptoms were classified using ACR nomenclature and case definitions [20]. Renal parameters (urinalysis, urine microscopy, urine protein to creatinine ratio (UPCr) and estimated glomerular filtration rate (eGFR)) were extracted at baseline and at LN diagnosis. UPCr and eGFR were analyzed as continuous variables. UPCr > 0.5mg/mg was sub-classified as a dichotomous outcome with ≥ 2mg/mg as nephrotic range proteinuria and < 2 mg/mg as sub-nephrotic proteinuria. eGFR was calculated using the modified Schwartz formula which is a validated measure for patients aged 2 to 18 years [21]. eGFR < 90mL/min/1.73m^2 was indicative of decreased renal function [22].

We defined LN as the presence of persistent UPCr > 0.5mg/mg, ≥ 3+ proteinuria and/or a renal biopsy demonstrating LN. Time of LN diagnosis was categorized as within the first 6 months from baseline, between > 6 months to ≤ 12 months from baseline or > 12 months to ≤ 24 months from baseline. LN classification was based on the 2003 International Society of Nephrology/Renal Pathology Society criteria for renal biopsy [23]. We sub-classified the six broad classes into mild (Class I or II only) and severe renal disease (Class III, IV, V, VI or any combination of Class V with other classes). The use of immune-directed therapy prior to

time of cSLE diagnosis was analyzed as a dichotomous variable for rituximab, cyclophosphamide, intravenous immunoglobulin (IVIG) and corticosteroids.

Statistical Analyses

We carried out descriptive statistics for all variables of interest including demographic, clinical, and laboratory variables. We summarized continuous variables as means and standard deviations and/or medians and interquartile ranges. We calculated counts and percentages for categorical variables. Differences in continuous variables were tested using two sample t-tests or Wilcoxon rank sum test for non-normal measures. Differences in categorical variables were tested using chi-square tests or Fisher's exact test for expected counts less than 5. All analyses were performed in SAS v 9.4 (Cary, NC). We used a statistical significance level of $p < 0.05$.

Association of autoimmune cytopenia at baseline and 2-year LN risk—Among all cSLE patients, we compared characteristics between patients with autoimmune cytopenia at baseline to other cSLE patients. Univariate and multivariable logistic regression models were developed with the outcome of LN to identify the independent and adjusted association between the presence of autoimmune cytopenias and LN. Variables with univariate associations with incident LN showing p-values < 0.2 as well as our covariates of interests (age at cSLE diagnosis, sex, ethnicity, race, the presence of anti-dsDNA, and prior use of immune-directed therapy) were included as candidate predictors in the initial model. Forward selection strategies were used to produce the final model using an a priori list of confounders.

Sensitivity Analysis

We planned a sensitivity analysis a priori to re-analyze our data excluding those patients with less than 2 years of follow-up to assess if the observed association of autoimmune cytopenia and 2-year LN risk still held.

RESULTS

We identified 397 patients with ICD-9 or ICD-10 codes corresponding to SLE between January 1, 2000 and June 30, 2016 from our medical records. Our final study population had 130 incident cases of cSLE without LN at baseline (Figure 1).

Demographic, clinical and laboratory characteristics of final study population at baseline

Our final population was predominantly female. Table 1 summarizes the demographic, clinical and laboratory characteristics of 130 incident cSLE patients. We had a predominantly black population. There were also 23 (19%) non-Hispanic white, 7 (6%) Asian, 10 (8%) Hispanic and 1 (1%) mixed race/native American patients.

The 43 patients with autoimmune cytopenia included 13 patients who were pretreated for autoimmune cytopenia (8 for ITP, 4 for AIHA and 1 with ES).

Comparison of final study population at baseline by autoimmune cytopenia status—As shown in Table 1, there was no significant difference in sex, race or mean age at baseline comparing those with autoimmune cytopenia to those without. When we compared differences in serologic markers, there was no meaningful difference in the frequency of positive anti-dsDNA antibodies between those with autoimmune cytopenia and those without. Patients with autoimmune cytopenia had a higher frequency of elevated erythrocyte sedimentation rate (45% versus 36% p=0.003). There were no statistically significant differences in eGFR, SLEDAI-2K or low C3 and C4 complements.

Comparison of final study population at baseline by race—When we compared black patients versus patients of other races, females were still the predominant sex in both groups and there was no statistically significant difference in mean age at baseline. Black patients had fewer oral ulcers (16% versus 34% p=0.025) but higher frequency of positive anti-RNP (67% versus 39% p=0.003), and anti-Smith (70% versus 33% p= <0.001) antibodies.

Comparison of final study population at baseline by age and by sex—In our study, 15 of 129 children were aged less than 9 years. Mean age of patients less than 9 years at baseline was 7 (SD 1) and 13 (SD 2) in patients 9 years or older. The younger patients had a higher frequency of fever than the older patients (73% versus 38% p=0.009). There were no statistically significant differences in eGFR or SLEDAI-2K. There were also no statistically significant differences in race, age, clinical or laboratory features comparing females to males.

Association of autoimmune cytopenia at baseline and 2-year LN risk

The 2-year incidence proportion of LN was 12% in our study population. As shown in Table 1, the 2-year risk of LN was lower in patients with autoimmune cytopenia (7%) compared to those without autoimmune cytopenias (15%), but this difference was not statistically significant.

As shown in Table 2, in our univariate analysis, examining the association of patient characteristics with incident LN, the odds of developing LN in patients with autoimmune cytopenia at baseline were 0.43 lower than the odds of developing LN in those without autoimmune cytopenia at baseline (95% CI 0.12, 1.60, p=0.204). The odds of developing LN in patients with low C3 at baseline were 3.81 times higher than the odds of developing LN in those without low C3 at baseline (95% CI 1.01, 14.42, p=0.049).

Autoimmune cytopenia at baseline and low C3 at baseline were included in our final multivariable logistic regression model. We lost 8% of patients when we used complete case analysis following list-wise deletion. After adjusting for the presence of autoimmune cytopenia at baseline, the odds of developing LN in low C3 patients at baseline were 4.24 times higher than the odds of developing LN in those without low C3 at baseline (95% CI 1.10, 16.34, p= 0.036).

Association of autoimmune cytopenia at baseline and LN severity

Table 3 summarizes the characteristics of the 16 patients who developed lupus nephritis within the 2-year follow-up period. At baseline, 3 of these 16 patients had autoimmune cytopenia. When we compared these patients to those without autoimmune cytopenia at baseline, we found no statistically significant difference in age, baseline eGFR or SLEDAI-2K (all $p > 0.05$). We also found no statistically significant difference in eGFR or UPCr at the time of LN diagnosis (all $p > 0.05$). Two of the 3 patients with autoimmune cytopenias had isolated class V LN; those without autoimmune cytopenia who had only 1 case of isolated class V LN.

Association of immune-directed treatment for autoimmune cytopenia prior to cSLE diagnosis and 2-year LN risk

Table 1 summarizes the prior immune-directed treatment received. Mean interval from rituximab administration to cSLE diagnosis was 6 months (SD 5.30). Median interval from IVIG administration to cSLE diagnosis was 4 months (IQR 51). Corticosteroids were mostly administered with rituximab or IVIG. None of the 13 patients who had prior immune-directed treatment for autoimmune cytopenia developed LN. Of the 30 patients who had autoimmune cytopenia but did not receive prior immune-directed treatment, 3 (10%) developed LN. Of the 87 other cSLE patients without autoimmune cytopenia at baseline, 13 (15%) developed LN. However, the difference in risk of LN among these three groups of patients was not statistically significant ($p = 0.41$).

Sensitivity analysis

When we re-analyzed our data excluding those patients with less than 2-year follow-up, the 2-year risk of LN was 8% in patients with autoimmune cytopenia compared to 15% in those without autoimmune cytopenia ($p=0.036$).

DISCUSSION

Our primary objective was to compare cSLE patients with autoimmune cytopenias to those without autoimmune cytopenias. Overall, our study found clinically relevant differences to support prior adult studies that SLE patients with autoimmune cytopenias may be a distinct sub-population from other patients with SLE [5–7].

We examined the first 2 years after cSLE diagnosis because this is when LN is more likely to develop. The relatively lower 2-year risk of LN we found in cSLE patients with autoimmune cytopenias is similar to earlier reports from adult studies that showed lower incidence and prevalence of LN in this subset of patients. We did not find that the presence of anti-dsDNA, or other commonly tested serologic markers, at the time of cSLE diagnosis were associated with LN risk. While 29% of our study population had low eGFRs at cSLE diagnosis, and low C3 at cSLE diagnosis was associated with an increased 2-year risk of LN, we did not find differences in eGFR or low C3 between patients with autoimmune cytopenias and those without autoimmune cytopenias to suggest that these factors are associated with their different LN risk. Similarly, we did not find a difference in SLEDAI-2K index or low C4 at cSLE diagnosis between the two subgroups to explain the

difference in LN risk. However, we noted that cSLE patients with autoimmune cytopenias had more neuropsychiatric disease but less arthritis, malar rash and myositis than those without autoimmune cytopenias. Erythrocyte sedimentation rate (ESR) is a non-specific marker of ongoing systemic inflammation and was higher in the patients with autoimmune cytopenias compared to the other patients. It is known that ESR may be elevated in the presence of anemia which likely contributed to this observation here since at the time of cSLE diagnosis, the SLEDAI-2K, which is a measure of overall disease activity, was similar between the two groups.

Prior reports showed that adult patients with autoimmune cytopenias had less severe renal involvement [5, 7]. Our study showed that of the 16 cSLE patients who developed lupus nephritis, those with autoimmune cytopenias at cSLE diagnosis had mostly isolated Class V, while those without autoimmune cytopenias, had mostly Class III and IV LN. While our inference is limited by the small number of patients who developed LN, this observation should be further explored as Class III and IV LN are associated with a higher risk of progression to end-stage renal disease. More so, there is evidence to suggest that pathologic mechanism in Class III and IV LN may differ from pure Class V LN [24].

We examined whether some of the decreased risk of LN in autoimmune cytopenia could be attributed to prior immune-directed treatment. Interestingly, our study showed that none of the 13 cSLE patients with autoimmune cytopenia who received immune-directed treatment prior to cSLE diagnosis developed LN. In comparison, the 2-year risks of LN for those with autoimmune cytopenia and cSLE who did not receive pre-treatment and for cSLE patients without any autoimmune cytopenia were 10% and 15%, respectively. The absence of LN in cSLE patients with autoimmune cytopenia who were pre-treated, suggests that early treatment may play a role in preventing development of LN and warrants further investigation.

Our results add to the growing discussion on phenotypic heterogeneity in cSLE [25]. While larger studies are needed, we raise important considerations regarding how disease drivers in cSLE patients with autoimmune cytopenias may differ from those without autoimmune cytopenias, and the impact of such mechanism on LN. Our focus on red blood cell and platelet cytopenias is relevant as both of these cellular subtypes are actively involved in the systemic inflammation that occurs in cSLE [26–31]. Recent blood transcriptome analyses of cSLE patients found a strong correlation between neutrophil signature and the presence of LN [24]. Similarly, another gene expression study of adult and pediatric SLE patients found neutrophil-driven clusters to be associated with an increased risk of proliferative LN [32]. However, the association of autoimmune cytopenias with these molecular stratifications, and particularly the risk of LN, has been under explored.

In our study, we were uniquely able to describe a population of 130 patients without LN at cSLE diagnosis. Two-thirds (66 %) of our patients were black. Our population had a mean age at cSLE diagnosis of 12 years, which is similar previous reports [33, 34]. Our female: male ratio of 4.65:1 was similar to reports from the large cSLE cohort studies from France and Toronto [34, 35]. Also, arthritis, fever and malar rash were the most commonly occurring clinical features. Nasal ulcers and discoid rash were uncommon. Black patients had

statistically significant higher frequency of positive anti-RNP and anti-Smith antibodies, as has been previously reported [36–39]. However, we did not find higher positive anti-SSA/SSB antibodies as reported by others [33]. We did not find many differences in cSLE manifestation by age, though younger children had more fever. It is thought that factors such as younger age and age-related physiologic changes in the kidney may independently contribute to increased risk of LN. However, there was no difference in the 2-year risk of LN or decreased eGFR at cSLE diagnosis in our study when we compared the two age groups. We also found no statistically significant sex differences in clinical and laboratory features or 2-year risk of LN. Interestingly, 29% of our patients presented with some renal insufficiency though they did not have persistent proteinuria to suggest LN. This renal insufficiency did not differ by autoimmune cytopenia status, age at cSLE diagnosis, race or sex.

A major strength of our study is that it was conducted on a predominantly black pediatric lupus population. We were able to examine age, sex and racial/ethnic differences and we approached renal outcomes in cSLE from a hematologic perspective. To the best of our knowledge, we are the first to examine the association of pre-treatment with immune-directed therapy for autoimmune cytopenia on renal outcomes within the first 2 years of cSLE diagnosis.

Our study has some limitations. While it was a relatively large single-center study on cSLE, we had a low 2-year incidence proportion of LN and so our study was underpowered to detect statistically significant differences in risk and severity of LN and prior therapy effects. Also, it was a retrospective study and we were limited to using the available data. Our study spanned a 16-year period during which there were differences in physician practice in obtaining laboratory and imaging data to evaluate for cSLE. A single center study may limit generalizability. However, there are no other pediatric rheumatology or nephrology practices in the Atlanta metropolitan statistical area and thus most cSLE patients are seen at our practice. Therefore, we have a representative sample population. Our center does not routinely perform activity or chronicity scoring of kidney biopsies which would have added more information about LN severity. Finally, we had a short follow-up period of 2 years, but more than 80% of LN develop within the first 2 years of cSLE diagnosis [2].

In conclusion, our findings indicate that patients with autoimmune cytopenia before or at cSLE diagnoses have statistically significant and clinically relevant differences from other cSLE patients. Our study highlights the need for further studies to understand the inherent and external factors contributing to these differences, and understand the impact of prior exposure to immune suppressing therapy on cSLE phenotype.

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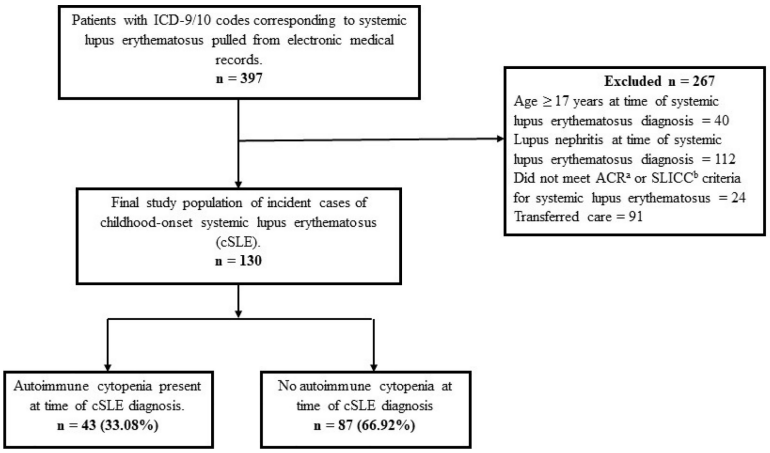

Figure 1:

Flow diagram showing selection of study population

Abbreviations: [a]ACR = American College of Rheumatology: [b]SLICC = Systemic Lupus International Collaborating Criteria for Systemic Lupus Erythematosus

Table 1.

Demographic, clinical and laboratory characteristics of incident patients with childhood-onset systemic lupus erythematosus from January 1, 2000 to June 30, 2016.

	All cSLE (n=130) N (%)	cSLE with AC (n=43) N (%)	cSLE without AC (n=87) N (%)	P-value	Missing
Demographics					
Sex					
Female	107 (82)	35/43 (81)	72/87 (83)	0.848	
Race				0.620	8
Black	81 (66)	26/41 (63)	55/81 (68)		
Other	41 (34)	15/41 (37)	26/81 (32)		
Age in years at cSLE diagnosis (mean (SD))[c]	12 (3)	13 (3)	12 (3)	0.321	
Clinical features					
Fever	54 (42)	21/42 (50)	33/87 (38)	0.193	1
Malar rash	47 (36)	10/42 (24)	37/87 (43)	**0.038**[S]	1
Photosensitivity	47 (36)	13/42 (33)	34/87 (39)	0.369	1
Discoid lupus[a]	3 (2)	1/42 (2)	2/87 (2)	1.000	1
Vasculitic rash	33 (26)	13/42 (31)	20/87 (23)	0.331	1
Raynauds[a]	14 (11)	5/42 (12)	9/87 (10)	0.770	1
Oral ulcers	31 (24)	9/42 (21)	22/87 (25)	0.631	1
Nasal ulcers[a]	4 (3)	2/42 (5)	2/87 (2)	0.596	1
Alopecia	21 (16)	4/42 (10)	17/87 (20)	0.149	1
Arthritis	64 (50)	13/42 (31)	51/86 (60)	**0.003**[S]	2
Angioedema[a]	8 (6)	2/41 (5)	6/86 (7)	1.000	3
Pleural effusion	26 (31)	12/32 (38)	14/53 (26)	0.283	45
Pericardial effusion	17 (32)	7/19 (37)	10/34 (29)	0.578	77
Neuropsychiatric symptoms[a]	8 (6)	6/43 (14)	2/87 (2)	**0.016**[S]	
Myositis[*]	20 (29)	2/20 (10)	18/49 (37)	**0.026**[S]	61
Laboratory features					
Positive ANA ≥ 1:40	130 (100)	43 (100)	87 (100)		
Positive anti-dsDNA ≥ 1:10	88 (70)	31/43 (72)	57/83 (69)	0.692	4
Positive anti-RNP[*]	72 (58)	24/43 (56)	48/81 (59)	0.711	6
Positive anti-Smith[*]	71 (57)	22/43 (51)	49/81 (61)	0.318	6
Positive anti-SSA[*]	56 (45)	20/43 (47)	36/81 (44)	0.826	6
Positive anti-SSB[*]	20 (16)	10/43 (23)	10/80 (13)	0.123	7
Leukopenia ≤ 4,000/uL	59 (46)	21/43 (49)	38/85 (45)	0.658	2
Lymphopenia ≤1,500/uL	81 (66)	29/42 (69)	52/81 (64)	0.591	7
Neutropenia ≤1,500/uL	32 (27)	14/42 (33)	18/79 (23)	0.210	9

	All cSLE (n=130) N (%)	cSLE with AC (n=43) N (%)	cSLE without AC (n=87) N (%)	P-value	Missing
Low C3 complement *	63 (53)	25/41 (61)	38/79 (48)	0.180	10
Low C4 complement *	78 (65)	29/41 (71)	49/79 (62)	0.343	10
ESR in mm/hr (mean(SD))	63 (41)	80 (45)	55 (36)	**0.003**^{S}	19
eGFR < 90mL/min/1.73m2	32 (29)	14/39 (36)	18/73 (25)	0.210	18
SLEDAI-2k (median(IQR,range)	9 (7 – 12)	9 (6 – 11)	10 (7 – 12)	0.655	11
Prior Treatment					
Corticosteroids^{a}	10 (8)	10/43 (23)	0/87 (0)	**<0.001**^{S}	
Cyclophosphamide	0 (0)	0/43 (0)	0/87 (0)		
IVIG^{a}	7 (5)	7/43 (16)	0/87 (0)	**<0.001**^{S}	
Rituximab^{a}	2 (2)	2/43 (5)	0/87 (0)	0.108	
2 year risk of lupus nephritis after cSLE diagnosis	16 (12)	3/43 (7)	13/87 (15)	0.190	
Follow-up period in years (mean(SD))	4.03 (2)	3.96 (2)	4.16 (2)	0.641	

Abbreviations: AC = Autoimmune cytopenias; cSLE = childhood-onset systemic lupus erythematosus; dsDNA = double-stranded DNA; ESR = Erythrocyte sedimentation rate; eGFR = Estimated glomerular filtration rate; IVIG = intravenous immunoglobulin; RNP = ribonucleoprotein; SLEDAI-2k = Systemic Lupus Erythematosus Disease Activity Index 2000; SS = Sjogren syndrome-related antigen

^{S} = significant with p value < 0.05

* By laboratory reference range, Comparisons were by chi square test except otherwise stated

^{a} Fisher's exact test

^{b} Wilcoxon rank sum test

^{c} Student's t-test

Table 2:

Univariate logistic regression analysis examining the association of patient characteristics with incident lupus nephritis (in the 130 cSLE patients without lupus nephritis at baseline).

Characteristics	Odds ratio	95% CI for Odds ratio	P-value
Presence of autoimmune cytopenia at cSLE diagnosis	0.43	0.12, 1.60	0.204
Age at cSLE diagnosis (in years)	0.99	0.83, 1.18	0.888
Sex (female versus male)	0.92	0.24, 3.54	0.906
Race (Black versus other)	2.20	0.59, 8.29	0.243
Arthritis	0.56	0.19, 1.64	0.290
Myositis *	3.07	0.85, 11.07	0.086
Positive anti-double-stranded DNA *	1.84	0.49, 6.94	0.367
Positive anti-ribonucleoprotein *	1.52	0.49, 4.73	0.474
Positive anti-Smith *	2.25	0.67, 7.49	0.188
Positive anti-SSA *	1.98	0.66, 5.95	0.744
Positive anti-SSB *	0.77	0.16, 3.71	0.224
low C3 complement at cSLE diagnosis *	3.81	1.01, 14.42	**0.049** ***S***
eGFR < 90mL/min/1.73m2 at cSLE diagnosis	2.92	0.93, 9.15	0.066
SLEDAI-2K at cSLE diagnosis (per 1 point in score)	0.98	0.86, 1.11	0.740

Abbreviations: cSLE = childhood-onset systemic lupus erythematosus; ESR = Erythrocyte sedimentation rate; eGFR = Estimated glomerular filtration rate; SLEDAI-2k = Systemic Lupus Erythematosus Disease Activity Index 2000; SS = Sjogren syndrome-related antigen

S = significant with p value < 0.05

* By laboratory reference range

Table 3.

Comparing characteristics of patients who developed lupus nephritis within the first 2 years of diagnosis by baseline autoimmune cytopenia status.

Characteristics	All cSLE* (n = 16) N (%)	cSLE with AC (n = 3) N (%)	cSLE without AC* (n =13) N (%)
LN by class[a]			
II	3/15 (20)	0/3 (0)	3/12 (25)
III	2/15 (13)	0/3 (0)	2/12 (17)
IV	5/15 (33)	1/3 (33)	4/12 (33)
V	3/15 (20)	2/3 (67)	1/12 (8)
IV/V	2/15 (13)	0/3 (0)	2/12 (17)
LN severity[a]			
Mild i.e. Class I and II only	3/15 (20)	0/3 (0)	3/12 (25)
Renal characteristics at time of LN diagnosis			
eGFR < 90mL/min/1.73m^2[a]	6/15 (40)	1/3 (33)	5/12 (42)
UPCr ≥2 mg/mg[a]	10/16 (63)	3/3 (100)	7/13 (54)
RBC casts at time of LN diagnosis[a]	1/16 (6)	0/13 (0)	1/13 (8)
Hematuria >5RBC/hpf[a]	12/16 (75)	1/3 (33)	11/13 (85)
Interval of LN from time of cSLE diagnosis in months			
>1 to ≤ 6	6/16 (38)	1/3 (33)	5/13 (39)
> 6 to ≤ 12	3/16 (19)	0/3 (0)	3/13 (23)
> 12 to ≤ 24	7/16 (44)	2/3 (67)	5/13 (39)

Abbreviations: AC = Autoimmune cytopenia; cSLE = Childhood-onset systemic lupus erythematosus; eGFR= Estimated glomerular filtration rate; LN= Lupus nephritis; UPCr = Urine protein to creatinine ratio

[a]Fisher's exact test

*Missing 1 patient without kidney biopsy