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BRIEF REPORT

Systemic lupus erythematosus nephritis and COVID-19 disease

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Abstract

Of the more than 20 studies published on SLE patients with COVID-19, none of the studies focused on lupus nephritis. We report the outcomes of renal biopsy-proven systemic lupus erythematosus (SLE) nephritis patients after COVID-19 disease. Our institute has been declared as a state COVID-19 hospital in the last week of March 2020. From then till now, we have admitted and managed COVID-19 patients from several districts of Andhra Pradesh and neighbouring states. We collected the data of patients with SLE nephritis contemporaneously from admission to the outcomes on a computerised proforma. We had identified sixteen patients with SLE nephritis who were admitted with COVID-19 disease. Of them, fourteen were females and two were males. The mean age was 29.3 years. Out of sixteen patients, seven required a mechanical ventilator and dialysis and eventually succumbed. One more patient died due to disseminated tuberculosis. Our results suggested that with an approximately 50% mortality rate, the COVID-19 disease had a calamitous effect on SLE nephritis patients.

Key Points

- *We identified the significant risk factors for mortality: younger age, higher serum creatinine at presentation, higher CT severity score and lower serum albumin.*
- *After the analysis done for this article, we decided to reduce the medications for SLE nephritis to prednisolone 10 mg/day when COVID-19 disease is contracted.*

Keywords Anti-dsDNA titre · COVID-19 disease · Dialysis · Nephritis · Renal biopsy · Systemic lupus erythematosus

Introduction

The predisposition to the infections for the patients with systemic lupus erythematosus (SLE) is because of the aberrant immune responses inherent to the disease and also due to the effects of treatment with steroids, immune-suppressants and immune-modulator drugs. The severity and the disease outcomes of the COVID-19 in SLE could be affected by the aberrant cellular, humoral and cytokine immune responses like lymphopenia, greater proinflammatory cytokines like IL-6 and abnormal B and T cell responses [1].

As COVID-19 emerged as a global threat, the early studies on patients with SLE and COVID-19 were from the heaviest hit regions. More than 20 studies have been published on SLE and COVID-19 [2]. Of the more than 20 studies published on SLE patients with COVID-19, none of the studies focused on lupus nephritis. The majority of the studies had large numbers of patients with SLE, with few confirmed COVID-19 disease [2]. We report the outcomes of renal biopsy-proven SLE nephritis patients after COVID-19 disease.

Material and methods

Sri Padmavathi Medical College Hospital, SVIMS University, was ordained as the state COVID hospital on March 28, 2020. From then till now, we have managed COVID-19 patients from several districts of Andhra Pradesh and neighbouring states.

In this study, we included SLE nephritis patients who had COVID-19 disease. There was no exclusion criterion. We collected the data of patients with SLE nephritis from admission to the outcomes on a computerised proforma. We included the demography, clinical features, laboratory data and treatment schedules of SLE nephritis and COVID-19 disease in the proforma.

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All patients had serum creatinine, blood urea, serum sodium and serum potassium, complete haemogram, liver function tests, anti-dsDNA antibody level, complement factor 3 and factor 4, prothrombin time and partial thromboplastin time, serum procalcitonin, serum ferritin, C-reactive protein, serum IL-6 and serum D-dimer sent on the first day of admission. Before COVID-19 disease, our patients had 24-h urine protein values, and during COVID-19 disease, only urine protein creatinine ratio could be quantified.

At our institute, SLE nephritis, class IV, is treated with injection methylprednisolone, 15 mg/kg/day for 3 days, followed by oral prednisolone, started at 0.5 mg/kg/day and tapered over 6 months, and injection cyclophosphamide, 500 mg to 1000 mg/sqm of body surface area once a month for 6 months. In the maintenance phase, the patients are given oral prednisolone and either mycophenolate mofetil, azathioprine or injection cyclophosphamide in quarterly doses for three doses.

Our institute has a standard treatment protocol for COVID-19 disease patients. We initiated all patients from admission on injection remdesivir 200 mg on day 1, followed by 100 mg from day 2 to day 10, injection dexamethasone 8 mg per day iv for 10 days, and low molecular weight heparin and vitamins. We included injection dexamethasone in our treatment protocol after the last week of July 2020.

We prescribed injection tocilizumab (Cipla Ltd.) when the serum IL-6 was elevated 10 times the reference range of our lab. We prescribed injection tocilizumab at 8 mg/kg per dose, up to a maximum dose of 400 mg. Likewise a total of two doses were prescribed. The State Government of Andhra Pradesh supplied all medications, including the injection tocilizumab.

We employed the following statistics: for the data of continuous variables and categorical variables, the Student *t*-test and chi-squared tests were used, respectively. For the risk factors for mortality, univariate linear regression was used. We used Medcalc, free online software.

We obtained the approval of the institute ethics committee. The number is 1204.

Results

Data of all COVID-19 patients

On March 28, 2020, our institute was designated as a state COVID-19 hospital. From then till December 31, 2021, we had admitted and managed 15,719 COVID-19 patients. The mortality rate was 18.3% (2878 deaths in 15,719 patients).

Data of SLE nephritis patients with COVID-19 disease

We had more than 125 SLE nephritis patients on regular follow-up. We identified sixteen patients with SLE nephritis admitted with COVID-19 disease till December 31, 2021. Of those, two patients were from different facilities. Of them, fourteen were females and two were males. The mean age was 29.3 years. These patients were diagnosed with SLE nephritis 10.3 months ago. All sixteen patients had renal biopsy-proven SLE nephritis prior to contracting COVID-19 disease. We noted that the SLE nephritis histological class was class IV in ten patients, class III + V in four patients and class V in two more patients. The median duration of symptoms of COVID-19 disease before admission was 2 days. The SPO_2 at admission was 90.8 ± 6.9%. The mean body mass index was 22.6 ± 1.2 kg/m^2.

Of these patients, seven were on current treatment with prednisolone and cyclophosphamide for a recent renal biopsy-proven nephritis and another seven were on minimal doses of combinations of prednisolone, mycophenolate mofetil and azathioprine. One of the remaining two was a 17-year-old girl with SLE nephritis class IV, diagnosed before COVID-19, who had presented with haematuria after the diagnosis of COVID-19. A repeat renal biopsy done during COVID-19 disease revealed cellular crescents in four out of eight glomeruli. The activity index: 12/24 and chronicity index: 2/12. We treated the patient with injection methyl prednisolone and dialysis. After 2 weeks, we shifted her to non-isolation wards for continuation of treatment with cyclophosphamide. After 3 months of follow-up, she was still on dialysis. The data of the last patient, a 19-year-old girl, was described below.

We present the data of renal parameters and disease activity of SLE in Table 1. Table 2 presents the data of parameters related to COVID-19 disease.

Outcome

The parameters related to SLE nephritis (Table 1) were better during and after COVID-19 disease, probably because some of the patients were on current immunosuppression.

Out of sixteen patients, seven patients, a male aged 23 years and six female patients aged between 15 and 31 years, required mechanical ventilator owing to worsened hypoxia and high respiratory rate. The CT severity scores of these seven patients were 12/25, 14/25, 15/25, 18/25, 20/25, 24/25 and 25/25, respectively. All seven patients required dialysis and eventually succumbed. Of these, six patients were on current treatment with prednisolone and cyclophosphamide.

Table 1 Parameters related to systemic lupus erythematosus nephritis

Parameter	Result before COVID-19 disease	Result during/after COVID-19 disease
Anti-dsDNA titre (reference range: >40 WHO IU/mL—positive)	163.8 ± 30.3	147.6 ± 23.0
Complement C3 (reference range: 91–156 mg/dL)	70.9 ± 8.9	81.0 ± 7.6
Complement C4 (reference range: 20–50 mg/dL)	18.4 ± 2.1	21.3 ± 4.5
Serum creatinine (mg/dL) in patients without renal failure ($n = 8$) (mean ± SD) (range)	1.17 ± 0.20 (0.9–1.4)	1.32 ± 0.22 (1.05–1.24)
24-h urine protein (g/day) in patients without renal failure ($n = 8$) (mean ± SD) (range)	2.1 ± 0.5 (1.4–3.2)	–
Urine protein creatinine ratio in patients without renal failure ($n = 8$) (mean ± SD) (range)	–	2.6 ± 0.8 (1.8–3.4)
Serum creatinine (mg/dL) in patients with renal failure ($n = 8$) (mean ± SD) (range)	7.82 ± 3.25 (3.5–12.1)	9.0 ± 3.0 (6.1–11.9)
24-h urine protein (g/day) in patients with renal failure ($n = 8$) (mean ± SD) (range)	0.8 ± 0.19 (0.7–1.1)	–
Urine protein creatinine ratio in patients with renal failure ($n = 8$) (mean ± SD) (range)	–	0.5 ± 0.1 (0.3–0.6)
Renal biopsy in SLE patients admitted with COVID-19 ($n = 16$)	Class IV: 10 Class III + V: 4 Class V: 2	Class IV: 1*
Blood pressure (mmHg) (mean ± SD) ($n = 16$)	144 ± 12/96 ± 7	158 ± 14/103 ± 6
Treatment of SLE nephritis	Steroids, cyclophosphamide and ACE inhibition	Steroids

*A 17-year-old girl with SLE nephritis class IV diagnosed before COVID-19 presented with haematuria after the diagnosis of COVID-19. A repeat renal biopsy done during COVID-19 disease revealed cellular crescents

Table 2 Parameters related to COVID-19 disease

Parameter	Result
Duration of symptoms of COVID-19 (median) (days)	2
SPO_2 at admission (%) (mean ± SD) ($n = 16$)	90.8 ± 6.9
Oxygen requirement during COVID-19 disease	10: oxygen by non-rebreather mask 2: non-invasive ventilation 4: mechanical ventilator
CT severity score at admission (range)	7.3 ± 0.94 (6–8)
CT severity score during hospital stay (day 5 after admission) (range)	13.66 ± 1.24 (6–15)
CRP (range) (g/L)	112.14 ± 106.05 (5.6–328)
S. ferritin (range) (ng/L)	555.6 ± 287.2 (265–960)
LDH (range) (mg/dL)	428 ± 86.5 (340–725)
Serum IL-6 (range) (pg/mL)	60.75 ± 52.08 (17–145)*

*One patient with serum IL-6 145 pg/mL had been given injection tocilizumab

One of them, a 31-year-old patient, had serum IL-6 145 pg/mL and was given an injection tocilizumab.

Another patient, a 19-year-old girl with class IV SLE nephritis, admitted with COVID-19 disease, had also been diagnosed with disseminated tuberculosis immediately after discharge from COVID-19 isolation wards. For SLE nephritis, she received injection methylprednisolone, followed by oral prednisolone and injection cyclophosphamide. She was in maintenance phase with oral prednisolone and mycophenolate mofetil. She had pleural effusion, cervical lymphadenopathy and bone marrow granulomas. The pleural fluid was lymphocyte dominant, the Light's criteria of pleural fluid suggested exudate, and pleural fluid adenosine deaminase was 53 U/mL. A cervical lymph node biopsy showed caseating granuloma. She succumbed after 3 weeks.

Out of the remaining eight patients, seven were discharged from COVID-19 wards and had been on regular follow-up at the nephrology outpatient service. The mean serum creatinine at the time of discharge of these seven patients was 1.32 ± 0.22 mg/dL. The last patient was on dialysis.

We identified the patients who succumbed were of younger age, had higher serum creatinine at presentation, higher CT severity score and lower serum albumin as factors which had a significant effect on mortality (Table 3).

Table 3 Risk factors for mortality

Parameter	Mortality	No mortality	*p*
Number of patients	8	8	–
Age (years/mean)	20.8	34.6	0.049*
Hypertension (%)	10 (5) (%)	4 (2) (%)	0.375
High serum creatinine (%)	10 (5) (%)	6 (3)	0.017*
Obesity (%)	2 (1) (%)	2 (1) (%)	1.000
CT severity score during hospital stay (day 5 after admission) (range)	10.66 ± 2.84 (6–15)	6.05 ± 1.41	0.037*
Haemoglobin (g/dL)	8.8 ± 2.3	8.6 ± 1.08	0.086
Total leucocyte count (per cu mm)	11,347.3 ± 5185.4	10,227.7 ± 3902.8	0.473
Platelet count (per cu mm)	2.1 ± 0.94	2.3 ± 1.04	0.702
Serum creatinine (mg/dL) (mean ± SD) (range)	5.81 ± 1.78 (3.5–12.1)	1.32 ± 0.21 (0.9–1.4)	0.0014*
S. albumin (g/dL)	2.5 ± 0.2	3.5 ± 0.2	0.0057*
CRP (g/L)	112.14 ± 106.05	95.61 ± 79.02	0.603
S. ferritin (ng/L)	555.6 ± 287.2	453.9 ± 288.3	0.310
Serum IL-6 (pg/mL)	60.75 ± 52.08	52.10 ± 32.07	0.428
Anti-dsDNA titre (reference range: >40 WHO IU/mL—positive)	163.8 ± 30.3	187.2 ± 18.5	0.251
Complement C3 (reference range: 91–156 mg/dL)	70.9 ± 8.9	69.1 ± 11.3	0.335
Complement C4 (reference range: 20–50 mg/dL)	18.4 ± 2.1	20.7 ± 1.1	0.891

* significant

Discussion

The present report provides data on sixteen patients with SLE nephritis who were admitted with COVID-19 disease. There were fourteen females. Out of sixteen patients, seven required a mechanical ventilator and dialysis and eventually succumbed. One more patient died due to disseminated tuberculosis.

The first studies on patients with SLE and COVID-19 emanated from the regions where early phases of the pandemic appeared. These were mostly case reports or small case series [3–5].

Mathian et al. [6] described 17 patients with SLE most of whom were on tablet hydroxychloroquine (HCQS) and affected with COVID-19 disease. Of those, seven (41%) patients required admission to an intensive care unit, and 2 out of 14 hospitalised patients died of COVID-19 disease. This study was one of the first to note that patients with SLE on HCQS were not protected against COVID-19.

Gartshteyn et al. [7] published the first patient series of patients with SLE and COVID-19 from the USA. The study included 18 patients, of which ten patients had COVID-19 infection confirmed by nasopharyngeal swab COVID-19 RT-PCR. The other eight patients had clinical symptoms highly suggestive of COVID-19 but were not tested. Seven of these patients were hospitalised, three of whom had severe hypoxemic respiratory failure. One patient improved and two remained critically ill. The remaining patients who were hospitalised improved without any requirement for supplemental oxygen. Most patients (83%) in this patient series were taking immunosuppressants, 39% were on steroids, and 61% had lupus nephritis.

Fernandez-Ruiz et al. [8] reported from the US epicentre, New York University. In this study, a total of 226 SLE patients were included. Of them, 41 with confirmed COVID-19, 19 who tested negative for COVID-19, 42 with COVID-19–like symptoms who did not get tested and 124 who remained asymptomatic without testing. Notably, no SLE-specific factors, such as immunosuppressant use, were noted to increase the odds of hospitalisation. Hospitalised patients tended to be older, non-white and Hispanic and had a higher body mass index, a history of nephritis and at least one comorbidity.

A few more studies have reported that the main risk factors for poor COVID-19 outcomes were similar to those in the general population, like age and the presence of comorbidities [5, 9–11].

Additional potential risk factors suggested by studies of SLE and other autoimmune diagnoses include the presence of interstitial lung disease, moderate or high rheumatic disease activity (or flare preceding the COVID-19 diagnosis), history of neuropsychiatric lupus and known exposure to a confirmed COVID-19 patient [12–14].

As alluded to before, none of the more than 20 studies published on SLE patients with COVID-19 focused on lupus nephritis. The majority of the studies had large numbers of patients of SLE with few confirmed COVID-19 disease, and only in two studies [7, 15] large number of SLE patients had more than 50% confirmed COVID-19 disease. However, in

another study [8], the confirmed number of COVID-19 disease patients was substantial.

An analysis of 13 studies [6–8, 15–24], which had reasonable data available, revealed 152 SLE patients with confirmed and presumptive COVID-19 disease. The mortality rate for them is 12 (7.89%).

In an aggregated analysis [25], 48 patients from 24 articles had been included. Patients with lupus nephritis were significantly more prone to developing severe to critical disease ($p = 0.036$) with an odds ratio of 5.40 (95% confidence interval of 1.120–26.045).

One of the limitations of the present study was that the values of anti-dsDNA, complement factor 3 and 4 prior to the COVID-19 disease were in fact the values of patients at their last follow-up. Understandably, the admission due to the COVID-19 disease was unpredictable.

The mortality rate of all COVID-19 disease patients at our institute was 18.3% (2878 deaths in 15,719 patients). In comparison, approximately 50% of mortality in SLE nephritis patients suggested the calamitous effect of the COVID-19 disease on SLE nephritis. Analysis revealed that the greater risk of mortality in younger patients was owing to the fact that the majority were on current immunosuppressive therapy. After this analysis, we decided to reduce the medications for SLE nephritis to prednisolone 10 mg/day when COVID-19 disease is contracted.

Author contribution C. Gayathri: collected patient data. K. Monica: collected patient data. P. Aishwarya Lakshmi: involved in the management of patients. S. Mathini: involved in the management of patients. N. Prasanna Kumar: involved in the management of patients. Ram: main faculty who managed the patients; main author of the article. V. Siva Kumar: revised and reviewed the article.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication Obtained from the patients and their near relatives.

Disclosures None.

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