

Infectious Complications in Lupus Nephritis and Associated Factors: A Multicenter Study

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Abstract

Introduction: The prevalence of infections in patients with systemic lupus erythematosus ranges from 26% to 78%. Patients with systemic lupus erythematosus are particularly susceptible to infections due to a dysfunction of immune response and the immunosuppressive therapy. **Patients and method:** We carried out this study with the aim of describing the prevalence of infections in lupus nephritis and determining the associated risk factors. This was a multicenter, observational, retrospective, descriptive and analytical study over a 10-year period from November 1, 2010 to October 31, 2020. The study was carried out in the nephrology departments of six hospitals in Dakar. **Results:** During the study period, 98 patients were included. The mean age was 32.32 ± 11.33 years with a sex ratio of 0.21. Among the included patients, fifty-four (55.1%) had at least one infectious episode, of which 53.7% had 1 infection, 24.1% had 2 infectious episodes and 22.2% had 3 infectious episodes. The overall incidence was 55.1 infections per 100 patient-years. 57.2% of these infectious episodes occurred within the first six months after the lupus was diagnosed. The main sites of infection were urinary (30.7%), gastrointestinal (22.0%) and pleuropulmonary (16.5%). The incriminated germ was a bacterium in 78.18% of cases, a virus in 5.46%, a parasite in 9.09 and a fungus in 7.27. The most frequently germ found was *Escherichia coli* (29.09%). The evolution was marked by recovery in 93.4% of cases. Deaths occurred in 15 patients of which 33.3% were related to infections. Factor significantly associated with the onset of infection in multivariate analysis was the presence of a proliferative class of lupus nephritis ($p = 0.013$). **Conclusion:** Infections were common during lupus nephritis. The presence of a proliferative class was risk factors for infection.

Keywords

Lupus Nephritis, Infection, Proliferative Class

1. Introduction

The prevalence of infections in systemic lupus erythematosus (SLE) patients ranges from 26% to 78% [1] [2] [3]. Patients with SLE are particularly susceptible to infections due to a dysfunction of the innate and adaptive immune response associated with the disease, which is exacerbated by the immunosuppressive therapy used to treat the disease [4]. This explains the higher infectious risk of patients with SLE compared to the general population [5]. Infections are one of the main causes of morbidity and mortality during SLE, especially in case of lupus nephritis (LN). They are responsible for 15% to 40% of patient admissions and 30% to 50% of deaths [3] [6] [7]. The prevalence of infections in LN is not sufficiently described in sub-Saharan Africa. We carried out this study with the aim of describing the prevalence of infections in LN and determining the associated risk factors.

2. Patients and Methods

This was a multicenter, observational, retrospective, descriptive and analytical study over a 10-year period from November 1, 2010 to October 31, 2020. The study was carried out in the nephrology departments of 6 hospitals in Dakar (Aristide Le DANTEC hospital, Dalal Jamm hospital, Pikine hospital, Principal hospital, Ouakam military hospital, Roi Baudoin hospital). The study included all records of patients who were followed for LN. The diagnosis of LN was made by a concordant renal biopsy associated with a proteinuria/creatinuria ratio greater than 0.5 g/g or with an active urine sediment [8]. For each selected patient, the epidemiological, clinical, biological, histological, therapeutic and evolutionary data were studied. The data collected were entered from Excel software. The descriptive study was carried out with the calculation of the means \pm standard deviation [minimum, maximum] or medians for the quantitative variables and the calculation of the frequencies for the qualitative variables. Data analysis was performed using SPSS software (Statistical Package for Science Social) version 18. The means and percentages were compared using the chi-square test and the exact Fischer test, respectively, according to their conditions of applicability. Any difference less than 0.05 was considered statistically significant. For multivariate analysis, we used a binary logistic regression model and included in this model the variables that were significant in bivariate analysis. The significance level retained for all the statistical analyzes was at $p \leq 0.05$.

3. Results

Ninety-eight patients were included. The mean age was 32.32 ± 11.33 years with a female predominance and a sex ratio of 0.21. The average duration of follow-up was 25.40 ± 20.40 months. Forty-eight patients were known to have lupus prior to renal impairment. The mean glomerular filtration rate (GFR) was $89.88 \text{ ml/min} \pm 53.65$ and 27.6% of patients had renal failure. C-reactive protein was measured in 68 patients, it was positive in 27 patients (39.7%). The mean

serum albumin was 21.25 ± 9.67 mg/L. The mean protidemia was 54.03 ± 11.87 mg/l. The mean proteinuria was 4.11 g/24h ± 3.40 . Nephrotic syndrome was found in 58.2% of cases. Isolated class V was the most common, found in 34 cases (34.7%), class III + V in 24 cases (24.5%), class IV in 11 cases (11.2%) and class IV + V in 10 cases (10.2%), class II was found in 9 cases (9.2%), class III in 6 cases (6.1%) and class I in 4 cases (4.1%). Hydroxychloroquine (HCQ) was prescribed in 83.7% of patients, methylprednisolone (MTP) in 59.2% of patients, prednisone was prescribed in 95.9% of patients, cyclophosphamide (CYC) in 27.6% of patients; mycophenolate mofetil (MMF) in 38.8% of patients and azathioprine (AZA) in 27.6% of patients (**Table 1**). Eighty-one infectious episodes have been identified. Fifty-four patients (55.1%) had at least one infectious episode, of which 53.7% had 1 infection, 24.1% had 2 infectious episodes and 22.2% had 3 infectious episodes. The overall incidence was 55.1 infections per 100 patient-years. The median time to onset of infection was 8.90 months $\pm 13.13\%$ and 57.2% of these episodes occurred within the first six months after the lupus was diagnosed. The main sites of infection were urinary (30.7%), gastrointestinal (22.0%), pleuropulmonary (16.5%) and skin (13.2%) (**Figure 1**). The germ was identified in 60.43% of cases and it was a bacterium in 78.18% of cases. The most frequently found germs were *Escherichia coli* (29.09%) and *Staphylococcus aureus* (14.55%) (**Table 2**). Hospitalization was necessary in 27.5% of infectious episodes. The evolution was marked by recovery in 93.4% of cases. Deaths occurred in 15 patients (15.3%) of which 5 (33.3%) were related to infections. In bivariate analysis, the factors significantly associated with the onset of infection were elevated serum creatinine level on admission ($p = 0.027$), renal failure ($p = 0.005$), proliferative class of LN ($p = 0.001$), taking MTP ($p = 0.001$) and oral corticosteroid therapy ($p = 0.038$) (**Table 3**). Factors significantly associated with the onset of infection in multivariate analysis was the presence of a proliferative class of LN ($p = 0.013$) (**Table 4**).

4. Discussion

The prevalence of infections varies across studies. In our series, 55.1% of patients presented at least with one infectious episode. These results are similar to those of Ibn Abdelouahab [9] and Yin *et al.* [10] which were 61.6% and 49.3% respectively. In Australia, in the series by Feldman *et al.* [1], the prevalence was lower (25.7%) (**Table 5**). This difference is explained by the fact that Feldman *et al.* only considered severe infections. Infections can affect one or more organs at the same time. They affect the lung, skin and urinary tract in more than two thirds of cases [11] [12]. In our study, these three locations represented 60% of cases. The other locations (osteoarticular, central nervous system, endocardium...) were rare. Lupus itself predisposes to infectious complications. Indeed, some intrinsic factors are involved in this immunosuppression: decrease in chemotaxis and phagocytosis; functional asplenia [13]; hypocomplementemia by excessive consumption of the C3 and C4 fractions of the complement or congenital deficit

Table 1. Demographical and clinical characteristics of participants.

Variables	Effectives
Mean age (years)	32.32 ± 11.33
Age groups (years)	
<20	8 (8.2%)
20 - 40	60 (61.2%)
40 - 60	28 (28.6%)
>60	2 (2%)
Gender (%)	
Men	81 (82.7%)
Women	17 (17.3%)
Protidemia (g/l)	54.03 ± 11.87
Albuminemia (g/l)	1.25 ± 9.67
Azotemia (g/l)	0.62 ± 0.79
Serum creatinine (mg/l)	17.71 ± 23.77
GFR (ml/min/1.73m ²)	89.88 ± 53.65
Renal failure (%)	27 (27.6%)
Hematuria (%)	35 (35.7%)
Proteinuria (g/24h)	4.11 ± 3.4
Nephrotic syndrome (%)	57 (58.2%)
C3 hypocomplementemia (%)	5 (5.1%)
C4 hypocomplementemia (%)	6 (6.1%)
CH50 hypocomplementemia (%)	2 (2%)
Anti-DNA antibodies (%)	33 (33.6%)
ANA (%)	51 (52%)
Anti-Sm antibodies	24 (24.48%)
Classes (%)	
I	4 (4.1%)
II	9 (9.2%)
III	6 (6.1%)
III + V	11 (11.2%)
IV	24 (24.5%)
IV + V	10 (10.2%)
V	34 (34.7%)
VI	0 (0%)
Immunosuppressants (%)	
Corticosteroids	94 (95.9%)
CYC	27 (27.6%)
MMF	38 (38.8%)
AZA	27 (27.6%)
RTX	1 (1%)
Cyclosporine	2 (2%)

GFR = glomerular filtration rate, ANA = anti-nuclear antibodies, anti-Sm = Anti-Smith antibodies CYC = cyclophosphamide, MMF = mycophenolate mofetil, AZA = Azathioprine, RTX = rituximab.

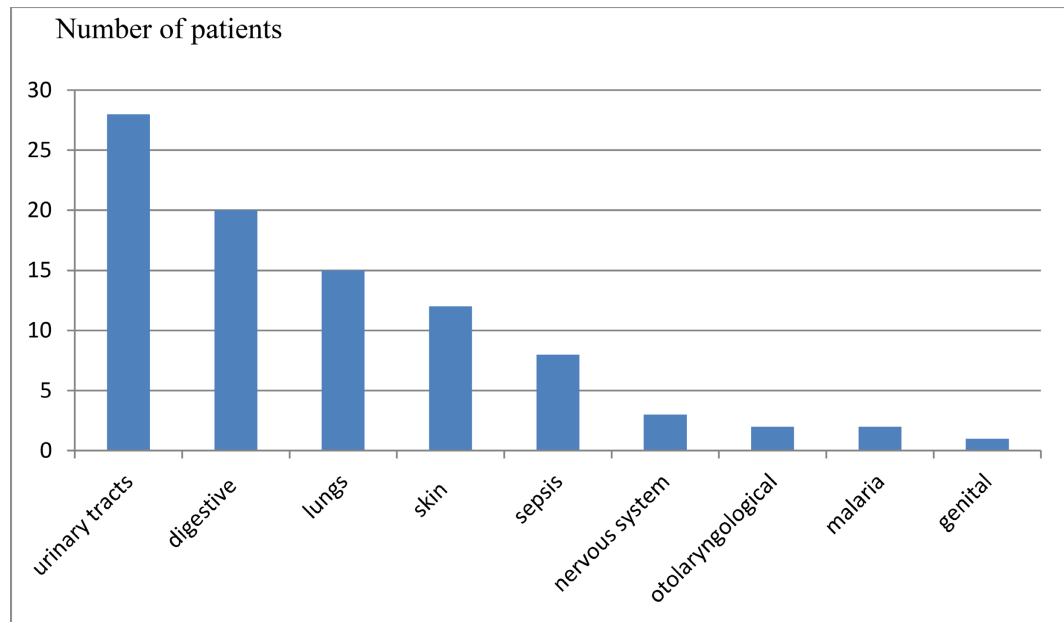


Figure 1. Distribution of patients according to the infectious site.

Table 2. Distribution of documented infections according to germs.

	Germs	Effectives	Percentages
Bacteria	<i>Escherichia coli</i>	16	29.09
	<i>Staphylococcus aureus</i>	8	14.55
	<i>Enterobacter spp</i>	5	9.09
	<i>Klebsiella pneumoniae</i>	3	5.45
	<i>Mycobacterium tuberculosis</i>	3	5.45
	<i>Streptococcus pneumoniae</i>	2	3.64
	<i>Meningococcus</i>	2	3.64
	<i>Citrobacter freundii</i>	1	1.82
	<i>beta-hemolytic Streptococcus</i>	1	1.82
	<i>Klebsiella pneumoniae</i>	1	1.82
	<i>Gardenerella vaginalis</i>	1	1.82
	Viruses	<i>Herpes zoster</i>	1
<i>varicella-zoster virus</i>		1	1.82
<i>Hepatitis B virus</i>		1	1.82
Parasites	<i>Plasmodium falciparum</i>	2	3.64
	<i>sarcoptes scabiei</i>	1	1.82
	<i>Trichomonas vaginalis</i>	1	1.82
	<i>Entamoeba histolytica</i>	1	1.82
Fungus	<i>Candida albicans</i>	4	7.27
Total		55	100%

Table 3. Bivariate analysis of risk factors for infection.

Variables	Infection (n = 54)	No infection (n = 44)	p
Gender (%)			
Women	45 (83.3%)	36 (81.8%)	0.844
Men	9 (16.7%)	8 (18.2%)	
Age groups (years)			
<20	5 (9.3%)	3 (6.8%)	0.365
20 - 40	35 (64.8%)	25 (56.8%)	
41 - 60	14 (25.9%)	14 (31.8%)	
>60	0 (0%)	2 (4.5%)	
Duration of follow-up (months)	28.72 ± 20.53	21.32 ± 19.70	0.074
Serum creatinine (mg/l)	22.55 ± 29.78	11.88 ± 11.20	0.027
Renal failure (%)	21 (38.9%)	6 (13.6%)	0.005
Nephrotic syndrome (%)	35 (64.8%)	22 (50.0%)	0.139
Leucopenia (%)	4 (7.4%)	6 (13.6%)	0.248
Lymphopenia (%)	21 (38.9%)	19 (43.2%)	0.667
ANA (%)	27 (93.1%)	24 (92.3%)	0.652
Anti-DNA antibodies (%)	16 (64.0%)	17 (68.0%)	0.765
C3 hypocomplementemia (%)	4 (57.1%)	1 (14.3%)	0.133
C4 hypocomplementemia (%)	4 (57.1%)	2 (28.6%)	0.296
Proliferatives classes (%)	37 (68.5%)	14 (31.8%)	0.001
HCQ (%)	44 (81.5%)	38 (86.4%)	0.515
MTP (%)	40 (74.1%)	18 (40.9%)	0.001
Prednisone (%)	54 (100.0%)	40 (90.9%)	0.038
MMF (%)	25 (46.3%)	13 (29.5%)	0.090
CYC (%)	19 (35.2%)	8 (18.2%)	0.061
AZA (%)	19 (35.2%)	8 (18.2%)	0.061

ANA = anti-nuclear antibodies, HCQ = hydroxychloroquine, MTP = methylprednisolone, CYC = cyclophosphamide, MMF = mycophenolate mofetil, AZA = Azathioprine, RTX = rituximab.

Table 4. Multivariate regression analysis of factors associated with infection.

Variables	Infection (n = 54)	No infection (n = 44)	OR	IC	p
Serum creatinine (mg/l)	22.55 ± 29.78	11.88 ± 11.20			NS
Renal failure (%)	21 (38.9%)	6 (13.6%)			NS
Proliferatives classes (%)	37 (68.5%)	14 (31.8%)	3.598	1.85 - 9.56	0.013
MTP (%)	40 (74.1%)	18 (40.9%)			NS
Prednisone (%)	54 (100.0%)	40 (90.9%)			NS

MTP = methylprednisolone; NS = not significant; OR = odds ratio; IC = interval of confidence.

Table 5. Incidence of infections reported by other studies.

Authors	Countries	Incidence of infections (100 patient-years)
Liu [21]	Singapore	17.6
Feldman [8]	United states	23.9
Mon [24]	Australia	18.4
Ibn Abdelouahab [9]	Morocco	35.5
Our series	Senegal	55.1

in certain fractions of the complement (C1r, C1s, C3 and C4) [14] [15]; polymorphism of MBL and osteopontin [11] [16] [17]; increased levels of Fc gamma III and GM-CSF levels [16], decreased cytotoxic activity of T lymphocytes (CD8) and the production of several factors having a major anti-infectious role (interleukins 1 and 2, interferons) [11].

Renal involvement also exposes to infectious complications due to immunosuppression caused by chronic renal failure and hypogammaglobulinemia in nephrotic syndrome. Other elements are frequently associated with the onset of infectious episodes. These are lymphopenia [18] and the use of immunosuppressive treatments (corticosteroids, azathioprine, cyclophosphamide, etc.) [14] [19] [20]. In our series, infections occurred in 57.1% of cases during the first six months of follow-up, coinciding with the period of induction therapy. These results agree with those of other studies in China (57.8%) [10] and Morocco (72.9%) [9]. The high prevalence during that period is explained by the fact that firstly the disease is more active during that period and secondly the immunosuppressive treatment is more intense during that period because it corresponds to the induction treatment. In our series, death occurred in 15.3% of cases, of which 33.3% of deaths were related to infectious causes.

This rate matches the one found in the series by Liu *et al.* [21] and Béji *et al.* [22] where infection was responsible for 43% and 38.8% of deaths, respectively. In the series by Ibn Abdelouahab [9] and Yap *et al.* [23], infectious complications were responsible for 66.6% and 50.5% of deaths, respectively, which is to be expected, since infections are one of the leading causes of death in LN. The proliferative class of LN was significantly associated with the onset of infection.

In a Moroccan study, Ibn Abdelouahab found that patients with proliferative LN had a significantly higher infection rate compared to patients with non proliferative LN [9]. This risk is explained by the fact that on one hand the proliferative classes are more severe and more active and on the other hand they require more intense immunosuppressive treatment than the non proliferative classes.

5. Conclusion

Infections were common during LN. The presence of a proliferative class was risk factors for infection.

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Author Contributions

Mansour Mbengue reviewed the literature and wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Limitations

The retrospective design of our study represents a limitation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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