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Clinical Presentation and Evolution of Systemic Lupus at the CNHU-HKM of Cotonou (Benin)

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a non-organ-specific autoimmune disease with an unknown origin. The unchanged trend of premature mortality in systemic lupus erythematosus shows the critical unmet need for improved and optimized management of systemic lupus erythematosus. **Objectives**: To analyze the clinical features and the prognostic factors of death in SLE at the CNHU-HKM of Cotonou. **Patients and Methods**: This was a retrospective cohort study. It was conducted over the period from January 1st 2010 to December 31st 2021. The study population consisted of all patients followed for SLE in the internal medicine, rheumatology, nephrology and dermatology wards at the CNHU-HKM of Cotonou. **Results**: 88 cases were recorded in 12 years, *i.e.* an incidence of 7 cases per year. There were 80 women and 8 men with a mean age of 36.4 ± 13.1 years. The clinical picture was dominated by mucocutaneous (86.3%) and osteoarticular (71.5%) disorders. The biological abnormalities observed were anemia (78.8%), lymphopenia (43.1%) and thrombocytopenia (17.7%). 39 patients had renal damage (44.3%). The incidence of death was 17%. Factors associated with death were renal involvement, infectious complications, high initial SLEDAI score, flare, thrombocytopenia and lymphopenia. **Conclusion**: Mortality related to SLE remains high at the CNHU-HKM of Cotonou. Renal involvement, infectious complications, high initial SLEDAI score, flare, lymphopenia and thrombocytopenia were the factors associated with death. The presence of these factors should lead to an evaluation of the treatment.

Keywords

Systemic Lupus Erythematosus, Death, Prognosis, CNHU-HKM

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which may affect almost any organ or system [1]. Mainly found in women of childbearing age [2], its etiology remains unknown, but probably involves complex interactions between hormonal, genetic and environmental factors [3]. The severity of lupus disease is linked not only to the various visceral manifestations, but also to the vascular risk due to chronic inflammation and long-term corticosteroid therapy. In Africa, epidemiological data show a mortality rate of 11% in Morocco in 2017, 11.7% in South Africa in 2016, and 43.1% in Cameroon in 2014 [4]. In Benin, the available data on lupus comes mainly from two studies based on relatively old data dating back 10 years. These studies showed that lupus is rare, with 33 cases in 14 years, a clinical polymorphism and a case-fatality rate in excess of 12% [5] [6]. These high mortality rates, despite the therapeutic advances of recent decades, highlight the need for improved and optimized disease management in hospitals. The aim of disease treatment is to preserve vital functions during severe relapses, counter the predictable evolution of visceral damage, prevent relapses and control symptoms to improve patients' quality of life. The aim of this study is to establish the clinical profile of lupus patients managed in Benin, to describe their evolution and to identify the main factors associated with death, in order to propose an appropriate management policy.

2. Study Framework and Methods

It was a retrospective cohort study, covering a 12-year period from January 1, 2010 to December 31, 2021. The study population consisted of all patients followed up for SLE in the internal medicine, rheumatology, nephrology and dermatology wards of the CNHU-HKM of Cotonou. The sampling procedure used was exhaustive registration. The diagnosis of systemic lupus erythematosus was based on the criteria of the American College of Rheumatology (ACR). Patients followed for at least 6 months after diagnosis were included. Patients with lost or incomplete medical records were excluded. The variables studied were those related to clinical features and evolution.

Variables related to the clinical presentation were sociodemographic (age, gender and occupation), clinical (general, cutaneous, osteoarticular, pleuropulmonary, cardiovascular and neuropsychiatric manifestations, etc.) and biological (immunological tests, blood count, sedimentation rate, C-reactive protein and renal test including 24-hour proteinuria). Outcome variables included treatment data, initial activity level according to SLEDAI criteria (no activity, mild, moderate or high activity, very high activity), response or relapse criteria according to SLEDAI at 6 months (severe relapse, moderate relapse, improvement or remission), complications observed during follow-up, death rate and main factors associated with death.

From an ethical point of view, a collection authorization was given by the hospital under number 1270/MS/CNHU-HKM/DAF/CSMR on August 17, 2022.

Confidentiality was also respected.

Data were collected using a pre-established survey form by the authors.

The form comprises 60 questions and was pretested to correct any imperfections.

Data analysis was performed using Epi-info and R version 4.1.2 software. Proportions were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Medians were compared using the Wilcoxon test with two independent samples. Univariate logistic regression was used to calculate the OR and its 95% confidence interval. A difference was considered significant if the p-value was less than 0.05).

3. Results

A total of 88 patients met the inclusion criteria. The mean age of the patients was 36.4 ± 13.1 years, with extremes of 14 and 68 years. There were 80 women (90.9%) and 8 men (9.1%), giving a sex ratio (M/F) of 0.1 (Table 1).

3.1. Clinical Data

Table 2 shows the main clinical manifestations observed in lupus patients. All these patients had at least one general symptom, mainly asthenia (71.6%). Skin manifestations were observed in 86.4% of patients, and were dominated by alopecia (59.1%) and erythema vespertilio (36.4%). Osteoarticular manifestations were observed in 71.6% of patients. Cardiac, pleuropulmonary and neuropsychiatric manifestations were less frequent, observed respectively in 18.2, 26.1% and 9.1% of patients.

3.2. Immunological and Other Biological Data

The main specific antibodies found were anti-nuclear antibodies (97.1%) and anti-native DNA antibodies (54.3%). Soluble anti-nuclear antibodies accounted for 77.1% of cases, while anti-Sm antibodies were found in 60% of patients (Table 3).

Table 1. Patient distribution by gender and occupation.

	Numbers	Percentage (%)
Sex		
Female	**80**	**90.9**
Male	**8**	**9.1**
Occupation		
Employee	**32**	**36.4**
Retailer	**23**	**26.1**
Student	**16**	**18.2**
Craftsman	**6**	**6.8**
Housewife	**6**	**6.8**
Student	**5**	**5.7**

Table 2. Distribution of lupus patients according to clinical manifestations at the time of diagnosis, CNHU-HKM, 2010-2021.

	Numbers	Percentage (%)
General symptoms	**88**	**100**
Asthenia	63	71.6
Weight loss	46	52.3
Fever	46	52.3
Anorexia	37	42.0
Cutaneous manifestations	**76**	**86.4**
Alopecia	52	59.1
Vespertilio erythema	32	36.4
Discoid lupus	16	18.2
Erythema outside malar region	14	15.9
Oral and pharyngeal ulcerations	12	13.6
Purpura	9	10.2
Photosensitivity	5	5.7
Raynaud's phenomenon	5	5.7
Livedo	1	1.1
Osteoarticular manifestations	**63**	**71.6**
Inflammatory arthralgia	58	65.9
Arthromyalgia	8	9.1
Joint stiffness	4	4.5
Non-erosive arthritis	2	2.3
Cardiovascular manifestations	**16**	**18.2**
Pericarditis	13	14.8
Myocarditis	1	1.1
Endocarditis	1	1.1
Pulmonary embolism	1	1.1
Heart failure	1	1.1
Pleuropulmonary manifestations	**23**	**26.1**
Pleuresis	15	17.0
Dyspnea	9	10.2
Cough	9	10.2
Neuropsychiatric manifestations	**8**	**9.1**
Psychiatric disorders (depression, psychosis)	3	3.4
Ischemic stroke	2	2.3
Convulsions	2	2.3
Tetraparesis	1	1.1
Paresthesias	1	1.1

Table 3. Distribution of lupus patients according to immunological profile, CNHU-HKM, 2010-2021.

	Numbers	Percentage (%)
Anti-nuclear antibodies	68	97.1
Anti-native DNA antibodies	38	54.3
Anti-RNP antibodies	27	77.1
Anti-SM antibodies	21	60.0
Anti-SSA antibody	18	51.4
Anti-SSB antibody	2	5.7
Anti-phospholipid antibodies	2	2.8
Rheumatoid factors	6	8.8
Anti-histone antibodies	6	8.8
Anti-nucleosome antibodies	4	5.7

The main biological abnormalities were accelerated sedimentation rate (100%), anemia (78.5%), elevated CRP (56.1%) and significant proteinuria (51.7%) (Table 4).

3.3. Therapeutic and Evolutionary Data

Table 5 shows the distribution of patients according to the main treatments received. Long-term treatment was mainly corticosteroids (86.6%) and hydroxychlo-roquine (79.5%), while biological treatments such as Rituximab were prescribed less frequently (1.1%) (Table 5).

The mean initial SLEDAI score was 9.3 +/− 5.4, with extremes of 2 and 31. At diagnosis, 17 patients (19.3%) had mild activity, 40 (45.5%) had moderate activity, 28 (31.8%) had high activity and 3 patients had very high activity. No patient presented without activity. At the end of six months, 45 patients (51.2%) were in remission, 15 (17.0%) were in moderate relapse, 7 (7.9%) had improved, 16 (18.2%) were stable, and 5 (5.7%) were in severe relapse. Figure 1 shows the distribution of patients according to SLEDAI score at 6 months.

Figure 2 shows the main complications found in the patients. Thirty-two patients (36.4%) developed complications. Complications were mainly infectious (23 patients), renal (20 patients), neuropsychiatric (11 patients) and pleuropulmonary (10 patients). Infectious complications were mostly of bacterial origin.

3.4. Death-Associated Factors

Table 6 shows the factors associated with mortality. In the whole cohort, 15 deaths were recorded at 6 months' follow-up, representing a case-fatality rate of 17.0%. Factors significantly associated with death were renal impairment ($p < 0.001$), infectious complications ($p = 0.001$; OR = 6.81), high initial SLEDAI score ($p < 0.001$; OR = 45.3), relapse ($p < 0.001$), lymphopenia ($p = 0.018$; OR = 4.46) and thrombocytopenia ($p = 0.023$; OR = 4). There were no deaths in patients who improved or remitted, or who had no renal impairment (Table 6).

Table 4. Distribution of lupus patients according to other biological disturbances.

	Numbers	Percentage (%)
Blood count (n = 79)		
Anemia	62	78.5
Lymphopenia	34	43.1
Thrombocytopenia	25	31.7
Leukopenia	14	17.7
Elevated CRP (n = 57)	**32**	**56.1**
Accelerated sedimentation rate (n = 84)	**84**	**100**
Renal tests		
Proteinuria > 0.5 g/24h (n = 56)	29	51.7
Elevated creatinemia (n = 76)	25	32.9

Table 5. Distribution of lupus patients by disease-modifying therapy.

	Numbers	Percentage (%)
Corticoids	76	86.6
Hydroxychloroquine	70	79.5
Dermocorticoids	15	17.0
Cyclophosphamide	8	9.1
Methotrexate	4	4.5
Azathioprine	2	2.3
Rituximab	1	1.1
Etanercept	1	1.1

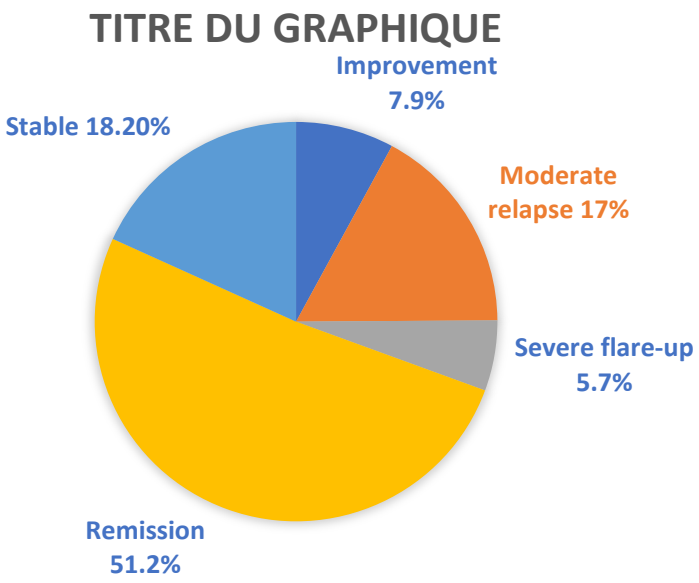

Figure 1. Distribution of patients according to SLEDAI score at 6 months.

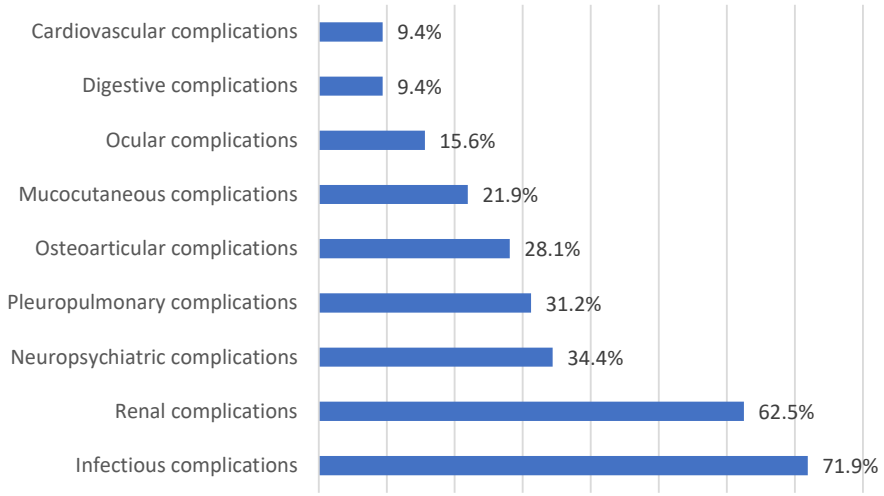

Figure 2. Distribution of patients by type of complication.

Table 6. Factors associated with patient death (univariate analysis).

	Death		p-valeur	OR (IC 95%)
	No, N = 73	*Yes, N = 15*		
Thrombocytopenia				
No	48	6	0.023	4 (1.2 - 13.9)
Yes	17	8		
Infectious complications				
No	59	6	0.001	6.8 (2.1 -23.7)
Yes	14	9		
High initial SLEDAI				
No	56	1	<0.001	45.3 (8.2 - 851)
Yes	17	14		
Kidney damage				
No	22	0	<0.001	
Yes	25	14		
SLEDAI at 6 months				
Improvement	7	0	0.065	
Flare-up	7	13	<0.001	
Remission	45	0	1	
Stable	14	2	0.065	
Lymphopenia				
No	41	4	0.018	4.4 (1.3 - 17.8)
Yes	24	10		

4. Discussion

We conducted a retrospective study. The absence of some data in certain medi-

cal files due to the retrospective nature of the study, and the exclusion of some incomplete files from the study, could constitute an information bias. In addition, due to the absence of social security coverage, certain follow-up check-ups and treatments were not carried out by the patients, even though they were indicated. Despite these limitations, we believe that this study provides sufficient information to improve the management and prognosis of lupus patients.

Lupus disease is common in young women. In our study, the sex ratio was 10 females for one male. That female predominance was described by F.Z. Elhattab in Morocco [7], whose sex ratio was 11 females for one male, and Diallo M.S *et al.* in Senegal [8], who found a sex ratio of 16 females for 1 male. The fact that the disease is predominantly female suggests a hormonal contribution. However, according to Weckerle *et al.*, it seems likely that many other types of gender-related genetic and immunological differences contribute to systemic lupus [9].

The mean age was 36.4 ± 13.1 years. Our results are similar to those of Besri Sophia in Morocco [10] and Diallo M.S [8] *et al.*, who found a mean age of less than 31 years. This average age also corresponds to the period of procreation, strengthening the hypothesis of the key role played by female reproductive hormones.

Mucocutaneous manifestations were noted in 86.4% of patients, dominated by alopecia (59.1%) and erythema vespertilio or malar rash (36.4%). The malar rash characteristic of SLE was observed in 56.25% of lupus patients by Kombate *et al.* at Lomé, Togo [11]. Jacyk *et al.*, in a South African, showed that malar rash is more frequent in white-skinned subjects [12]. Osteoarticular manifestations of inflammatory arthralgia (65.9% of cases) involved the elbow, knee, ankle, wrist and shoulder joints. This result does not differ from those of T. Ben Achour [13] in Tunisia, who found osteoarticular manifestations in 79.4% of patients. Compared with systemic diseases, joint involvement is the most frequent inaugural manifestation. Painful osteoarticular symptoms most often lead patients to consult internal medicine and rheumatology departments.

The main specific antibodies found were antinuclear antibodies in 97.1% of cases, and 54.3% were anti-native DNA antibodies. F.Z Elhattab *et al.* [7] reported 93.65% antinuclear antibodies in their study, and T.B Achour [13] found an average rate of 50% native anti-DNA antibodies. Anti-Sm antibodies were observed in 60% of patients in our study. Diallo MS *et al.* [8] reported 69.6% anti-Sm antibodies they studied. We also noted 51.4% anti-SSA antibodies. This result is similar to that of Diallo MS *et al.*, who found 54.4% anti-SSA antibodies. F.Z Elhattab *et al.* found 36.67% anti-SSA antibodies [7].

Biological disorders revealed also 78.5% of patients with anemia. This result is similar to those of Diallo MS *et al.* in Senegal [6], who found 74% haematological complications.

The treatments used were mainly corticoids (86.6%) and hydroxychloroquine (79.5%). This result is similar to those reported by Lehraiki Meriem in the internal medicine department of the CHU in Oujda, who had 87.5% use of synthetic antimalarials in combination with corticosteroids [14]. After six months,

51.2% of our patients were in remission, 17.0% were in moderate relapse, 7.9% had improved, 18.2% were stable, and 5.7% were in severe relapse. Mean overall survival was 81.5% in the series by Taylor H *et al.* [15] and Ka MM in Senegal [16]. Complications were mainly infectious (bacterial mainly), renal, neuropsychiatric and pleuropulmonary. This confirms the data in the literature that SLE can affect almost any organ or system, and testifies to the severity of the disease's prognosis.

In the cohort as a whole, 15 deaths were recorded after 6 months of follow-up, representing a death rate of 17.0%. This frequency is higher than those found in Europe [17], North Africa [18] and United States [19]. In sub-Saharan Africa, Teclessou *et al.* [20] and Daboiko *et al.* [21] reported death rates of 22.5% and 22.4% respectively. These results demonstrate the still high mortality associated with SLE in our black African countries.

Factors significantly associated with death were renal involvement ($p < 0.001$), infectious complications ($p = 0.001$; OR = 6.81), high initial SLEDAI score ($p < 0.001$; OR = 45.3), relapse ($p < 0.001$), lymphopenia ($p = 0.018$; OR = 4.46) and thrombocytopenia ($p = 0.023$; OR = 4). The association between renal involvement and death found in our study is in agreement with most authors who confirm that renal involvement is a poor prognostic factor in SLE. This is the case for Meunier *et al.* [22] in France ($p < 0.001$; OR = 3.29), Wang *et al.* [23] in China ($p = 0.032$; OR = 3.1); Bouras *et al.* [24] in Morocco ($p = 0.027$) and Wadee *et al.* [25] in South Africa ($p = 0.002$). Indeed, the prognosis of lupus patients is strongly influenced by the existence or absence of nephropathy secondary to lupus. In a large European cohort [26], it was shown that the ten-year survival rate from the discovery of lupus was 94% for patients without nephropathy versus 88% for those who entered the disease with proven lupus nephropathy. This difference appears to be amplified with longer follow-up, with proportions rising to 83% and 54% respectively after 20 years of lupus disease progression [27].

Infectious complications were also significantly associated with death in our cohort. The same was true for Mu *et al.* [28] in China ($p = 0.000$; OR = 4.25), Rabbani *et al.* [29] in Pakistan ($p = 0.004$), Bouras *et al.* [24] in Morocco ($p = 0.026$). Several studies have demonstrated that corticosteroids, especially at daily doses in excess of 20 mg, are responsible for increasing the risk of infection. However, even before the widespread use of corticosteroid therapy in SLE, infectious complications were reported with frequencies of up to 40% [30]. This confirms that, apart from the therapies used, SLE itself predisposes to opportunistic or non-opportunistic infectious complications. Indeed, certain intrinsic factors are involved in this predisposition: reduced chemotaxis and phagocytosis; functional asplenia; hypocomplementemia due to excessive consumption of complement fractions C3 and C4 or congenital deficiency in certain complement fractions (C1r, C1s, C3 and C4); reduced cytotoxic activity of T lymphocytes (CD8) and production of several factors with a major anti-infectious role (interleukins1 and 2, interferons) [30]. Moreover, in 2005 Whitelaw *et al.* [31] showed that even with specialized intensive care, infections are associated with high

mortality in SLE in South African public hospitals. These data prompt us to consider ways of reducing infectious morbidity in SLE. These can be dichotomized along two axes: optimizing the treatments we prescribe, and preventing infections, notably through vaccination.

There was also a significant association between a high initial SLEDAI score and death. In Tunisia, Jallouli *et al.* [32] reported that a high initial SLEDAI score was a poor prognostic factor ($p = 0.019$). Oubelkacem *et al.* [33] made the same observation in Morocco. Massardo *et al.* [34] in Chile reported that a SLEDAI score higher than 10 at diagnosis was a poor prognostic factor ($p < 0.001$). Several other authors agree that a high SLEDAI score, reflecting disease activity, is associated with high short-term mortality [35]. Indeed, uncontrolled disease activity leads to irreversible damage to target organs, which in turn increases the risk of premature death; early and sustained control of disease activity can usually be achieved with conventional immunosuppressive therapy [36].

Similarly, lupus relapse was significantly associated with death. Teh and Ling [37] reported in Malaysia that the simultaneous presence of a lupus relapse and infection was a poor prognostic factor for patients in their series (OR = 5.56). They also pointed out that the relapse was the cause of death in 19% of cases. Koh *et al.* [38] reported in South Korea that lupus relapse was responsible for death in 50% of cases. These data once again demonstrate the importance of well-managed disease-modifying therapy and regular, meticulous follow-up to control disease activity.

Among the biological characteristics, thrombocytopenia was predictive of fatal outcomes in our series. This result is in accordance with those of Jallouli *et al.* [32] in Tunisia ($p = 0.027$), Chen *et al.* [39] in China ($p < 0.001$; OR = 4.57) and Fernandez *et al.* [40] in the USA ($p < 0.001$).

Indeed, in addition to life-threatening hemorrhages resulting directly from low platelet levels, other serious manifestations of SLE occur more frequently in patients with thrombocytopenia. These include neuropsychiatric manifestations, hemolytic anemia, antiphospholipid syndrome and renal disease. Although patients with SLE rarely die from bleeding complications, these patients have a poorer prognosis [41]. Two studies of SLE showed that thrombocytopenia was the only, or almost the only, independent risk factor for early mortality in SLE [42] [43]. Lymphopenia was also a poor prognostic factor in our series. We did not find a study in the literature demonstrating the direct association of lymphopenia with death. However, several authors report that diseases causing lymphopenia are associated with an increased susceptibility to several infections [44] [45], which are known to be factors directly linked to mortality in SLE. Indeed, two studies have shown that lymphopenia in patients with SLE is associated with a high risk of infection [45] [46]. Moreover, Warny *et al.* [45] reported that the relative risk of infection-related death in patients with lymphopenia compared with those whose lymphocytes were within the reference range was 1.70 (95% CI: 1.37 - 2.10). These factors could explain the association between lymphopenia and death in our study.

5. Conclusion

SLE-related mortality is high at the CNHU-HKM in Cotonou. Factors significantly associated with death were renal damage, infectious complications, high initial SLEDAI score, relapse, thrombocytopenia and lymphopenia. In order to improve the prognosis of lupus patients, it is essential to improve the knowledge of caregivers and the technical platform for the diagnosis and appropriate management of lupus and its complications.

Conflicts of Interest

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

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