CLINICAL PROFILE AND RISK FACTORS OF MAJOR INFECTIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Nambiar Veettil Jayachandran¹, Liza Rajasekhar², Gumdal Narsimulu³

¹Associate Professor, Department of Medicine, Government Medical College, Calicut, Kerala, India.

²Professor and HOD, Department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.

³Former Professor and HOD, Department of Rheumatology, Nizam's Institute of Medical Sciences, GVN Medical Centre, Hyderabad, Telangana, India.

ABSTRACT

BACKGROUND

Infection is a major source of morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE). Prevalence of infections in SLE is much higher than in general population. Infection remains the most important practical problem while managing lupus patients, especially in developing countries. There are only few studies on clinical profile and risk factors of infections in SLE.

MATERIALS AND METHODS

This is a descriptive study. Hospitalised SLE patients with infections were examined for pattern of infections in SLE and they were compared with SLE patients without infections for demographic and the lupus related variables.

RESULTS

105 infection related admissions were compared with 118 infection unrelated admissions. A causative organism was identified in 79.6%. The pattern of infections was as follows: Gram negative infections (54.4%), fungal infections (24.4%), tuberculosis (8.8%) and gram-positive infections in 12.2%. Higher disease activity was seen in the infected group. The duration of prednisolone intake and hence the cumulative prednisolone dose prior to infection was significantly higher in infected group. Infection rate was not higher in the subgroup, which received other immunosuppressive drugs. The incidence of leukopenia and lupus nephritis was same in both groups.

CONCLUSION

Infections were common in SLE patients, especially in younger age and early part of the illness. Infections were associated with prolonged use of steroids and higher disease activity.

KEY WORDS

Systemic Lupus Erythematosus; Lupus; Infection.

HOW TO CITE THIS ARTICLE: Jayachandran NV, Rajasekhar L, Narsimulu G. Clinical profile and risk factors of major infections in systemic lupus erythematosus. J. Evolution Med. Dent. Sci. 2018;7(35):3868-3872, DOI: 10.14260/jemds/2018/866

BACKGROUND

Infection is a major source of morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE). Immunologic abnormalities reported in SLE are believed to contribute to the increased risk of infection.^[1] Immunosuppressive treatment is also believed to contribute to this risk. Review of data from many clinical series of SLE patients has revealed an incidence of infections ranging from 14 - 77%.^[2] Infections were 5 to 10 times more in lupus patients than in patients with nephrotic syndrome and rheumatoid arthritis.^[3]

Several studies attempting to identify risk factors for infection in SLE have yielded varying results. There is only one cohort study examining pattern of infections and risk

factors for infections in SLE from the Indian subcontinent.^[4] The present study compares hospitalised SLE patients with and without infection in an attempt to identify clinical or laboratory features differentiating the two groups.

Objectives of the Study

To study the characteristics of major infections in SLE and to compare demographic, disease and drug related variables in a cohort of hospitalised SLE patients with and without infection.

MATERIALS AND METHODS

Study Design

This is a descriptive study based on data collected already. Records of patients classified as SLE according to the 1997 revised criteria of the American College of Rheumatology (ACR)^[5] and admitted in the Department of Rheumatology, Nizam's Institute of Medical Sciences (NIMS) between 2003 and 2006 were studied.

Two groups of patients were identified. The first group consisted of hospitalised SLE patients who had evidence of at least one infection during their admission and the other group comprising of hospitalised patients with SLE who did not have infection during their admission.

Infection was confirmed by means of supportive clinical features and positive cultures and/ or response to antibiotic

'Financial or Other Competing Interest': None.

Submission 17-05-2018, Peer Review 10-08-2018,

Acceptance 16-08-2018, Published 27-08-2018.

Corresponding Author:

Liza Rajasekhar,

Professor and HOD,

Department of Rheumatology,

Nizam's Institute of Medical Sciences,

Hyderabad, Telangana, India.

E-mail: lizarajasekhar@gmail.com

nvjchandran@gmail.com

DOI: 10.14260/jemds/2018/866

therapy. As per usual standard of care all patients with SLE presenting with fever ($>38^{\circ}\text{C}$) were evaluated with chest radiograph, blood culture and urine culture, which were taken under strict aseptic measures prior to starting antibiotics. Culture negative cases were considered infected if there was an unequivocal clinical response to antibiotic therapy. CSF study and brain imaging were done if CNS infections were suspected. The diagnosis of tuberculosis was based on histology or cultures or a clinical picture specific for tuberculosis (e.g. hydrocephalus with meningitis, pulmonary apical infiltrates or miliary shadowing on chest radiograph. Infections diagnosed in the study were according to the definitions described by Mandell.^[6]

Infection was not entertained if supportive data were absent or if in the physician's opinion (LR, NVJ) the presence of infection was equivocal.

Potential Risk Factors for Infection analysed included-

1. Demographic Details: Age, duration of SLE on admission (time interval from diagnosis of SLE to the hospitalisation).
2. Disease activity at the time of admission as ascertained by SLEDAI, a well-validated instrument for assessing lupus disease activity. We took extreme care not to score proteinuria, haematuria, fever and leucopenia unless they were believed to be ongoing and due to lupus activity.
3. The laboratory variables including haemoglobin, leukocyte and lymphocyte count, anti-dsDNA, C3, C4, and serum albumin.

Statistical Methods

Data was analysed using SPSS Version 16.0. Variables between the two groups were compared using independent sample t-test and Mann-Whitney test.

RESULTS

Patient Characteristics

During the four-year period of study from January 2003 to December 2006, medical records pertaining to 177 patients with SLE were reviewed. Seven patients were males and 170 females. Mean duration of follow-up was 37.63 ± 43.47 months. The mean age was 27.15 ± 10.32 years.

There were 223 hospital admissions in 177 patients. 105 hospitalisations were assigned to the infected group and 118 hospitalisations to the uninfected group. In the infected group, infection was either the primary or secondary cause of admission. Only in 64 was infection clinically obvious at admission.

Characteristics of Infection

In the group of hospitalisations associated with infections ($n=105$), 113 infections were identified clinically or microbiologically. In 11 patients, infection was documented in more than one site concurrently. A causative organism was isolated in 90 of 113 infections (79.6%). In the rest, infection was diagnosed on the basis of unequivocal clinical features and/or response to treatment.

67% of all infections in which an organism was identified ($n=90$) were bacterial in origin. Gram negative organisms contributed to 54.4%, gram positive organisms in 12.2%, Fungus in 24.6% and mycobacterium in 8.8%. *Escherichia*

coli was the commonest organism identified (Table 1). Tuberculosis was identified in 8 patients. Lung and meninges were the common site of tuberculous infection. One patient had miliary tuberculosis. In all patients who developed tuberculosis, hike in the dose of steroids was noted a few months prior to the infection due to increased disease activity.

Blood stream infection was identified in 28 patients and urinary tract infections in 26 and respiratory tract infections in 26. Table 2 summarises the anatomic location of the infections.

Recurrent Infections

12 patients were admitted more than once with major infection in the four-year period of follow-up. Three of these patients had ongoing lupus nephritis. The mean SLEDAI in 26 such admissions in 12 patients was 10.58. In this group, 66% had low complement levels.

Comparison of Clinical and Biological Variables in the Two Groups

The results are summarised in Table 3. The patients in the infected group were younger. The duration of SLE at the time of admission was comparable between the groups. Disease activity as assessed by SLEDAI was significantly higher in the infected group.

The haemoglobin level and the platelet count were lower in the infected group. The mean leukocyte count was not different in the two groups. 55 patients had a leukocyte count below 4000/cu.mm. Twenty-two of these had an infection, while 33 patients did not have an infection at the time the leucopenia was documented. The total leukocyte count, the absolute lymphocyte count, serum albumin levels, serum complement levels and anti-dsDNA levels were not different between the two groups.

The renal involvement was comparable between the two groups. In the group without renal disease, the number of infected and uninfected patients was almost the same. 44 uninfected patients and 45 infected patients had renal involvement.

Disease Activity

Independent sample test showed that there was significant difference between the disease activities of the two groups as assessed by the SLEDAI. The infected group had a significantly higher SLEDAI score median 10 (IQR11) when compared to uninfected group 8 (9.5), $p=0.02$.

Immunosuppressive Therapy

Corticosteroids

The mean prednisolone dose in the last six months was not different between the two groups. However, the duration of prednisolone use was significantly longer in the infected group suggesting a higher cumulative steroid dose in the infected group.

Cyclophosphamide

The infection was related to cyclophosphamide if it occurred within two months after receiving a dose of cyclophosphamide. The average cumulative dose of cyclophosphamide used was 3000 mg given over 3 months.

In the infected group 20 out of 77 patients were exposed to cyclophosphamide prior to infection, whereas in the uninfected group also 27 out of 100 patients were exposed to cyclophosphamide (odds ratio= 0.95). In this subgroup of patients who were exposed to cyclophosphamide prior to infection, 27 infectious episodes were identified which included 16 gram-negative infections, 8 fungal infections and 3 gram-positive infections. Tuberculosis was conspicuous by its absence.

Methotrexate

In the infected group 7 out of 77 were exposed to methotrexate prior to infection, whereas in the uninfected group also 23 out of 100 were exposed to methotrexate, the Odds Ratio (OR) being 0.33. Three patients developed tuberculosis and 2 had salmonella infection.

Azathioprine

In the infected group 16 patients were exposed to azathioprine, whereas in the uninfected group 31 patients were exposed to the same (OR= 0.58). Six patients exposed to azathioprine group developed tuberculosis when compared to none in the cyclophosphamide group.

Methylprednisolone

Among the 18 patients who received pulse therapy with methylprednisolone prior to hospital admission, infections were recorded in 11 patients within 8 weeks of receiving methylprednisolone. Five had fungal infection of the oro-oesophageal mucosa, 1 had cryptococcal meningitis. The odds ratio of developing an infection soon after methylprednisolone was 3.16.

Mortality

Twelve SLE patients died during the hospital stay or soon after this period. In 5 patients, infection was the primary or secondary cause of death. In two patients, infection was the primary cause of death (Candida sepsis, MRSA sepsis).

Escherichia coli	22
Candida sp	20
Mycobacterium tuberculosis	8
Pseudomonas aeruginosa	7
Klebsiella pneumonia	7
Staphylococcus aureus	6
Salmonella sp	5
Streptococci pneumonia	3
Stenotrophomonas maltophilia	2
Enterococcus	1
Proteus mirabilis	1
Acinetobacter baumannii	2
Enterobacter aerogenes	1
Diphtheroids	1
Cryptococcus neoformans	1
Serratia marcescens	1
Alcaligenes xylosoxidans	1
Pneumocystis jiroveci	1
Total	90

Table 1. Frequency of Isolated Microorganisms

Infection Site	Number	%
Urinary tract	26	23.1
Lung	26	23.1
Gastrointestinal tract	13	11.5
Bacteraemia without focus	28	24.8
Skin	13	11.5
CNS	3	2.6
Musculoskeletal	3	2.6
ENT	1	0.8

Table 2. Anatomic Location of Infections in SLE Patients

Variable	Infected Group Median (IQR)	Uninfected Group Median (IQR)	P
Age (years)	22 (9)	27 (14)	0.005
Duration (months)	33 (38)	40 (53)	0.49
SLEDAI	10 (11)	8 (9.5)	0.02
ESR (mm/hr)	57 ± 43	54 ± 41	0.601
Prednisolone duration (days)	89.5 (75.75)	65 (73.5)	0.041
Prednisolone dose (mg)	20 (20)	10 (18.25)	0.33
Anti-dsDNA	210 (293)	210 (284)	0.88
C3	39 (48)	40.5 (55)	0.94
C4	8.3 (12.5)	6 (14)	0.339

Table 3. Comparison of Clinical Variables

DISCUSSION

NIMS is a university hospital and tertiary referral centre in the South East India. This descriptive study in hospitalised SLE patients provides information about the characteristics of patients, type of infection in SLE and the difference in clinical and laboratory variables in a cross-sectional Indian cohort of 177 patients.

The most important observation in our study is that the disease activity as measured by SLEDAI was significantly higher in patients during infection. The mean SLEDAI in the patients who had recurrent infections (12 of the cohort of 77 patients with a major infection in these four years) also was higher. This supports the previous reports that infections are strongly related to disease flares.^[7-9] It is possible that the ongoing immune dysfunction due to active lupus predisposed the individuals to infection, considering that none of the other variables were different in the two groups. Disease activity of SLE is an important risk factor for infections in SLE. Many abnormalities like deficiency of immunoglobulins and complement factors, defective chemotaxis and phagocytic function contribute to the increased susceptibility to infection.^[10]

Duffy et al in one of the early studies observed that disease activity was much higher in SLE patients admitted with infection irrespective of their steroid dose and duration.^[7] Petri showed that disease activity in the previous year, average prednisone dose of greater than 10 mg, immunosuppressive drug use, neurologic SLE and previous hospitalisation was associated with current admission for infection.^[8] Similar to Paton's observation, we found 11 major infections in patients in close chronology with methylprednisolone.^[9] Various other studies have showed an association of renal insufficiency,^[11,12] proteinuria^[13] or lymphopenia^[14] with infection in SLE patients. We could not find any statistically or clinically significant relationship

between these clinical parameters and infection. Presence of lupus nephritis also failed to show an influence on the incidence of infection. At the same time, there was no statistically significant difference in the complement levels between the two groups in our study.

Another important observation is the low prevalence of infection in patients exposed to cyclophosphamide. One study has reported a significant relationship between cyclophosphamide therapy and infection in SLE.^[15] However, in a recent prospective study, cyclophosphamide therapy alone did not constitute a risk factor for infection.^[16] Studies have shown that infections occurred frequently when cyclophosphamide was given orally, in patients with leucopenia and when given high-dose steroids.^[17] We have been using low-dose cyclophosphamide pulse therapy (500mg) for most of our patients with lupus nephritis and other major organ involvement for induction of remission followed with azathioprine for maintenance. This may be one reason for the low prevalence of infection in this subgroup.

Even though the mean dose of prednisolone was not different in the two groups, the duration of prednisolone use was significantly longer in the infected group. It has been shown that prolonged long-term steroid therapy results in impaired T-cell function and lymphopenia.^[18] This observation also implies that higher cumulative dose of prednisolone was a risk factor for infection in our cohort of hospitalised patients.

The pattern of infection was not significantly different from the other reported series from the rest of the world. Gram negative infections dominated followed by fungal and gram-positive infections. We studied infections in hospitalised SLE patients and therefore concentrated on major infections. This is the reason why minor infections including herpes zoster and upper respiratory infections do not find significant place in this report.

Tuberculosis is common in India. The prevalence of tuberculosis in India is reported as 5.05 per thousand. Prevalence of radiological disease has been estimated to be 1.3 - 1.9%.^[19] In a prospective follow-up of an Indian cohort of 309 SLE patients over 6 years, tuberculosis was reported as the commonest infection.^[4] In a study of 146 SLE patients from India, a prevalence rate of 11.6% was reported.^[20] In our cohort of hospitalised patients, a prevalence of 4.51% (8 infections in 177 patients admitted was noted. Tuberculosis was rare in the cyclophosphamide exposed group. Only prospective comparison of lupus patients on different immunosuppressive drugs will elucidate whether risk of reactivation of tuberculosis has any relation to a particular immunosuppressive drug.

CONCLUSION

This descriptive study comparing SLE patients with and without major infections found infected patients to be younger and having a shorter duration of SLE. Duration of prednisolone use was longer in this subgroup. Most interestingly, the infected group had a statistically significant higher disease activity.

ACKNOWLEDGEMENT

We acknowledge the help rendered by Prof. V Lakshmi, Department of Microbiology, Nizam's Institute of Medical Sciences, Hyderabad in carrying out the study.

REFERENCES

- [1] Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. *Semin Arthritis Rheum* 1996;25(5):318-36.
- [2] Petri M. Infection in systemic lupus erythematosus. *Rheum Dis Clin North Am* 1998;24(2):423-56.
- [3] Staples PJ, Gerding DN, Decker JL, et al. Incidence of infection in systemic lupus erythematosus. *Arthritis Rheum* 1974;17(1):1-10.
- [4] Shyam C, Malaviya AN. Infection-related morbidity in systemic lupus erythematosus: a clinico-epidemiological study from northern India. *Rheumatol Int* 1996;16(1):1-3.
- [5] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40(9):1725.
- [6] Mandell G, Bennett JE, Dolin R. Principles and practice of infectious diseases. 5th edn. Philadelphia: Churchill Livingstone 2000.
- [7] Duffy KN, Duffy CM, Gladman DD. Infection and disease activity in systemic lupus erythematosus: a review of hospitalized patients. *J Rheumatol* 1991;18(8):1180-4.
- [8] Petri M, Genovese M. Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort. *J Rheumatol* 1992;19(10):1559-65.
- [9] Paton NI, Cheong IK, Kong NC, et al. Risk factors for infection in Malaysian patients with systemic lupus erythematosus. *QJM* 1996;89(7):531-8.
- [10] Perez HD, Andron RI, Goldstein IM. Infection in patients with systemic lupus erythematosus. Association with a serum inhibitor of complement-derived chemotactic activity. *Arthritis Rheum* 1979;22(12):1326-33.
- [11] Yuhara T, Takemura H, Akama T, et al. Predicting infection in hospitalized patients with systemic lupus erythematosus. *Intern Med* 1996;35(8):629-36.
- [12] Gomez J, Palazon D, Ortega G, et al. Infections and systemic lupus erythematosus. Analysis of risk factors and prognosis. A prospective study 1979-1988. *Rev Clin Esp* 1991;188(2):72-5.
- [13] Massardo L, Martinez ME, Baro ME, et al. Infections in systemic lupus erythematosus. *Rev Med Chil* 1991;119(10):1115-22.
- [14] Ng WL, Chu CM, Wu AK, et al. Lymphopenia at presentation is associated with increased risk of infections in patients with systemic lupus erythematosus. *QJM* 2006;99(1):37-47.
- [15] Noel V, Lortholary O, Casassus P, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. *Ann Rheum Dis* 2001;60(12):1141-4.
- [16] Bosch X, Guilabert A, Pallares L, et al. Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients. *Lupus* 2006;15(9):584-9.

- [17] Pryor BD, Bologna SG, Kahl LE. Risk factors for serious infection during treatment with cyclophosphamide and high dose corticosteroids for systemic lupus erythematosus. *Arthritis Rheum* 1996;39(9):1475-82.
- [18] Boumpas DT, Chrousos GP, Wilder RL, et al. Glucocorticoid therapy for immune mediated disease: basic and clinical correlates. *Ann Intern Med* 1993;119(12):1198-208.
- [19] Udwadia Z. *Clinical Tuberculosis*. 2nd edn. Chapman & Hall 1998: p. 591-605.
- [20] Balakrishnan C, Mangat G, Mittal G, et al. Tuberculosis in patients with systemic lupus erythematosus. *J Assoc Physicians India* 1998;46(8):682-3.