Original Article

Prevalence of Common Infections and Flare-ups in on-treatment SLE Patients Attending Two Tertiary Care Hospitals in Kolkata

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Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease. Infections are the most common complications. Early detection, proper management of infection and its differentiation from Lupus flare are of paramount importance.

Objective : To find out the prevalence of infections with various etiologic agents among on-treatment SLE patients who were hospitalized for suspected infections and to differentiate infections from disease flare.

Methods : This was a cross-sectional observational study with 50 patients of more than 16 years of age of both sexes fulfilling the Systemic Lupus International Collaborating Clinics (SLICC) 2012, classification criteria of SLE who were admitted for suspected infection as manifested by fever and systemic symptoms. Specific tests to identify etiological agent for infection were performed and the condition was differentiated from lupus flare with the help of the tests such as Total Leucocyte Count (TLC), C-reactive Protein (CRP), Anti-ds DNA, complements-C3 and C4.

Result : Infections were evident in 42 patients (84%) with predominant monoinfection being pneumonia in 13 patients (30.9%) followed by Urinary Tract Infection (UTI) in 8 patients (19%). *Streptococcus pneumoniae* was the major cause of Pneumonia while *Escherichia coli* caused most of UTIs. The infection markers were fever, CRP and TLC. Of the 42 patients, 40 patients (95%) had fever, 28 (66.7%) had Leukocytosis and 35 (83%) had CRP 10 mg/L or more indicating infection. Anti-ds DNA antibody was raised in 4 patients out of total 6 patients with Lupus flare. The complements C3 and C4 values were low in all the 6 patients. No patient of disease flare had raised CRP or Leukocytosis

Conclusion : Among 50 on-treatment SLE patients who were admitted in two Tertiary Care Hospitals of Kolkata with suspected infection it was found that 42 patients were having infections and 6 patients were suffering from Lupus flare. The predominant monoinfection was Pneumonia followed by UTI.

[*J Indian Med Assoc* 2022; **120(1):** 22-5]

Key words **: Systemic Lupus Erythematosus, Infection, Lupus flare.**

Systemic Lupus Erythematosus (SLE) is an autoimmune disease in which cellular damage occurs by tissue-binding antibodies and immune complexes. The prevalence is highest in women of child-bearing age[1].

Infections and SLE :

Various infectious agents are involved in the pathogenesis of SLE due to abnormal production of autoantibodies. The potential mechanisms include (Fig 1)[2].

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Received on : 06/11/2021

Accepted on : 05/12/2021

Editor's Comment :

- SLE patients are usually maintained on disease remission with lowest possible dose of glucocorticoids mainly prednisolone and other immunosuppressants like Hydroxychloroquine, Mycophenolate Mofetil, Cyclophosphamide etc. They may come back with fever and other systemic symptoms of suggesting infections.
- Detection of specific infection is as important as diagnosing disease flare in this situation as the later is not very uncommon. Moreover disease flare is managed by increasing the dose of corticosteroids with or without addition of other immunosuppressant but infection is treated by use of appropriate antimicrobials.

Apart from these, infections are among the most common complications of SLE. The most serious organ disease that occurs in SLE is nephritis. Nephritis and infections are leading causes of mortality in the first decade of disease[1].

The pattern and etiology in various infections are very important. Pneumonia, UTI, Skin and Soft tissue infections are the most common infections for hospitalization of SLE patients and Bacteremia and Sepsis are the most common causes of in-hospital mortality.

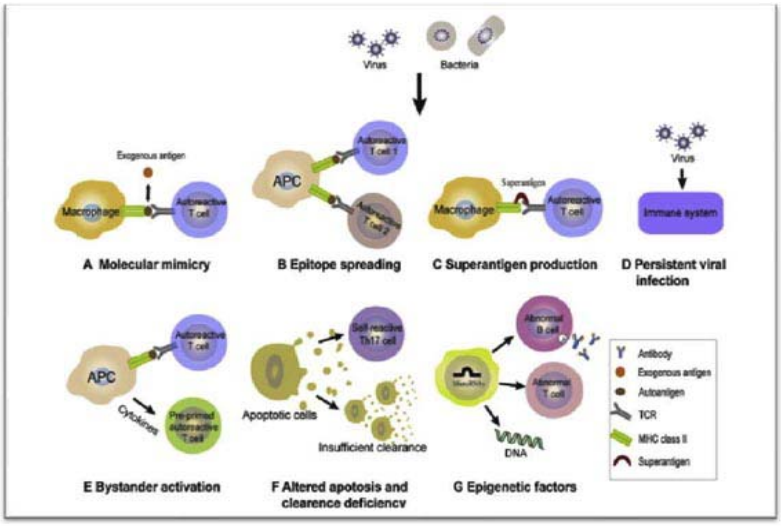

Fig 1

The risk factors for pre-disposition of SLE patients to various infections are: [3]

- Use of corticosteroids and other immunosuppressives
- Complement deficiencies
- Organ involvement such as kidney disease
- Functional hyposplenia
- Severity of disease activity.

Infecion and Lupus Flare :

A SLE patient with infection usually presents with fever with or without system specific signs and symptoms. However, a patient with increased disease activity denoting SLE flare also can present in a febrile state. Thus although it is difficult to distinguish an ongoing infection in SLE patient from a SLE flare, a clear distinction must be made as treatment of one is different from the other. An infection needs treatment with antimicrobials whereas in Lupus Flare, immunosuppressive agents are indicated. Several biochemical markers are used to distinguish between them[4].

Material and Method

This cross-sectional observational study was conducted in the Department of Tropical Medicine, School of Tropical Medicine and Department of Rheumatology, IPGME&R from July, 2019 to June, 2020. The aim of the study was to assess the prevalence of infection among SLE patients hospitalized for suspected infection to find out the sites and the causative organism of infection and to differentiate infection from disease flare.

The study included 50 patients of more than 16 years of age of both sexes fulfilling the SLICC 2012 classification criteria of Systemic Lupus Erythematosus who were regularly being followed up at OPD of above two hospitals and admitted for suspected infection manifested by fever and symptoms like headache, cough with or without expectoration, pain abdomen, diarrhea, vomiting, burning sensation during micturition. The patients with Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) co-infections, current or past malignancy within the past 5 years and pregnant or lactating women were excluded from the study. Predesigned proforma for data collection was used and informed consent was obtained. Detailed medical history, physical examination comprising of general survey and systemic examination and specific tests necessary for detection of infection were performed and TLC, CRP, Anti-ds DNA, complements-C3 and C4 were assessed to identify disease flare. Ethical clearance was obtained from Clinical Research Ethics Committee (CRE-STM), School of Tropical Medicine.

All the 50 patients recruited for study were getting maintenance dose of prednisolone as shown in Table 1.

Along with the maintenance dose of pre-dnisolone the recruited patients were also getting other immunosuppressive drugs like Table 2.

Observation

The following infections were detected among 42 patients who were diagnosed to have infections (Table 3).

Documented evidence of infection was obtained in 42 patients (84%) with the Predominant monoinfection being pneumonia in 19 patients (45.2%) followed by UTI in 8 patients (19%). The other

Table 1 — *Prednisolone dosage*

Prednisolone dosage	Number of patients (n=50)
5 mg	2
7.5 mg	24
10 mg	21
15 mg	2
20 mg	1

Table 2 — *Immunosuppressants*

Immunosuppressants	Number of patients (n = 50)
Mycophenolate mofetil	13
Hydroxychloroquine	50
Cyclophosphamide	7
Cyclosporine	0
Dapsone	2
Rituximab	3
Tacrolimus	1
Azathioprine	0

monoinfections which followed suit were Extrapulmonary Tuberculosis (EPTB) in 4 patients (9.5 %), cellulitis in 3 patients (7.1 %), oral candidiasis (OC) in 3 patients (7.1 %), pulmonary tuberculosis (PTB) in 2 patients (4.7 %) and 1 case each of Esophageal Candidiasis (EC) and Upper Respiratory Tract Infection (URTI). There were also evidence of mixed infections, Predominant being a combination of pneumonia and UTI in 3 patients (7.1%). There were 5 cases of EPTB with 4 of them as monoinfection out of which 3 had pleural effusions and 1 had Ascites. The patient with dual infection of EPTB and Scrub Typhus also had pleural effusion. There was a case of Pneumonia which progressed to Sepsis, a case of Pneumonia with cellulitis and another case of pneumonia with coinfection with Gluteal Abscess (Table 3).

Diagnosis of Pneumonia was supported by typical clinical features along with biochemical and radiological evidence of lung infection. Microorganisms causing Pneumonia were searched for and in a total of 19 cases of Pneumonia, 3 cases were due to *Streptococcus Pneumoniae* and 1 case each of *Pseudomonas Aeruginosa*, *Klebsiella Pneumoniae* and *Staphylococcus aureus*. Culture of sputum sample was done by VITEK method. In 13 cases no organism could be identified (Table 4).

Diagnosis of UTI in 11 patients was evident by typical symptoms of burning sensation during urination with increased frequency of urination in some along with evidence of pus cells in Routine Urine Examination. Urine culture revealed *Escherichia coli* as the commonest pathogen (6 patients) followed by 1 case of *Proteus Mirabilis* infection and 1 of *Enterobacter sp*. In 3 cases no organism could be identified.

The markers of infection were presence of fever along with rise in CRP values and Total Leucocyte Count. In our study out of the 42 patients with infection,

Table 3 — *Types of infection*

Infection	Number of patients (n=42)
Cellulitis	3
Upper respiratory tract infection	1
Pneumonia	13
Extrapulmonary tuberculosis	4
Pulmonary tuberculosis	2
Urinary tract infection	8
Oral candidiasis	3
Esophageal candidiasis	1
Cellulitis with pneumonia	1
Extrapulmonary tuberculosis with scrub typhus	1
Pneumonia with bacteremia	1
Pneumonia with UTI	3
Pneumonia with gluteal abscess	1

Table 4 — *Microorganisms causing pneumonia*

Microorganism causing pneumonia	No of patients (n=19)
Streptococcus pneumoniae	3
Pseudomonas aeruginosa	1
Klebsiella pneumoniae	1
Staphylococcus aureus	1
No organism identified	13

40 patients (95%) had fever, 28 patients (66.7%) had leukocytosis and 35 patients (83%) had CRP values ≥10 mg/L indicating infection. Combination of the above markers is better than a single marker for diagnosis of infection (Fig 2).

The patients of suspected infection should be differentiated from disease flare. In our study subjects among 6 patients of Lupus flare the value of anti-ds DNA antibody was raised in 4 patients. The values of C3 and C4 complements were less than the normal in all the 6 patients. No patient had CRP value greater than 10 mg/L and no patient had Leukocytosis. 3 patients had the WBC count in the normal range while 3 patients had Leukopenia (Fig 3).

Discussion

In our study population of 50 patients a definitive diagnosis could be achieved in all the patients. 42 patients (84 %) had various types of infections and 6 patients had Lupus flare. One patient had Kikuchi's disease for which diagnosis was on the basis of Histopathology but the etiological agent could not be identified. One patient who presented with respiratory distress without fever had evidence of right lung middle lobe collapse on his chest radiography. The cause of the collapse was undiagnosed as the patient took discharge against medical advice.

Documented evidence of infection was obtained in 42 patients (84 %) with the predominant monoinfection being pneumonia in 19 patients (45.2%) followed by Urinary tract UTI in 8 patients (19%). The other

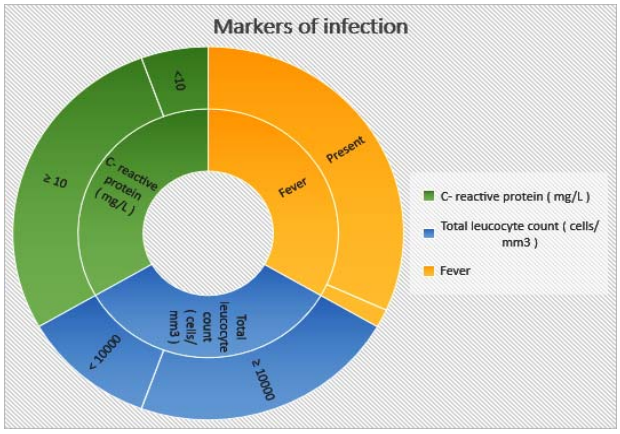

Fig 2 — Markers of infection

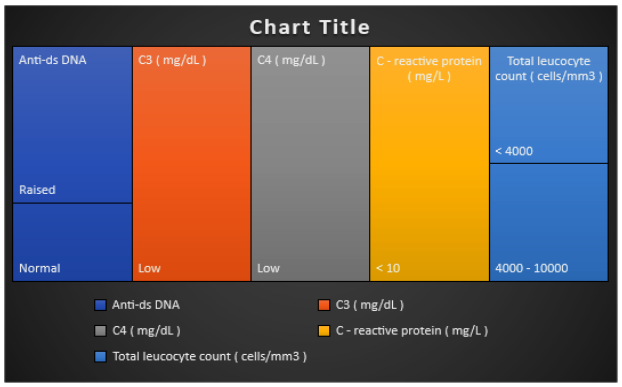

Fig 3 — Markers of lupus flare

monoinfections which followed suit were EPTB in 4 patients (9.5%), Cellulitis in 3 patients (7.1%), OC in 3 patients (7.1%), PTB in 2 patients (4.7%) and 1 case each of EC and URTI. There were also evidence of mixed infection, predominant being a combination of Pneumonia and UTI in 3 patients. There were 2 cases of mixed infection, one being Pneumonia and Cellulitis and another being Pneumonia and gluteal abscess. One of the cases of Pneumonia progressed towards bacteremia causing sepsis. There was one instance of EPTB who also had scrub typhus infection. Jung et al[4] found 120 cases of infection in his case-control study. Jeong *et al*[5] found predominant infection to be Pneumonia. Teh *et al*[6] also found the predominant infection to be Pneumonia followed by Septicemia. In a nested case control study by Ruiz-Irastorza et al[7] there were 83 instances of infection with most common being Pneumonia in 34 cases.

The patients who presented with symptoms and signs of suspected infection had to be differentiated from Lupus flare. The identifying markers of lupus flare were a raised anti-ds DNA antibody, low complements C3 and C4 and normal CRP and TLC.

The traditional markers of infection were presence of fever, high Leucocyte count and high CRP were used to provisionally diagnose patients with suspected infection and diagnosis was facilitated by radiological evidence and microbiological confirmation wherever possible. In our study out of the 42 patients with infection, 40 patients had fever, 28 patients had leukocytosis and 35 patients had CRP value ≥10 mg/L. A study by Jung *et al*[8] in 2017 reported high Leucocyte Count, high C-reactive Protein (CRP) and high ESR as the markers of infection.

In our study we found that out of the 6 patients with lupus flare, while all of them had low complements C3 and C4 and a normal CRP value, 4 patients had anti-ds DNA raised and in 3 patients Total Leukocyte Count (TLC) was normal while the rest 3 had Leukopenia. Jung *et al*[8] documented in his study suspected lupus flare over infection with reduced Leucocyte count and complements C3 and C4, elevated anti-ds DNA titre and no change in CRP levels.

Differentiating Lupus flare from infection is very much crucial as their treatments are different. A case of infection is treated by Antimicrobials but Lupus flare is controlled by immunosuppressives.

Limitation of our study :

Our study had a few limitations namely a small sample size, short time duration of the study and observational study design. The lack of a specific biomarker to differentiate infection from Lupus flare forced us to judge on the basis of conventional markers along with the clinician's decision for the diagnosis.

Thus there is need for further such studies with improved study design to determine risk factors for infection, early identification of infection and specific differentiating marker between infection and disease flare in SLE for an improved quality of life in these patients.

Conclusion

Among 50 on-treatment SLE patients who were admitted in two Tertiary Care Hospitals of Kolkata with suspected infection it was found that 42 patients were having various type of infections and 6 patients were suffering from Lupus Flare. The predominant monoinfection was Pneumonia followed by UTI.

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