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LUPUS FLARE

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Abstract :
Systemic lupus erythematosus, an autoimmune connective-tissue disorder with a wide range of clinical features, predominantly affects women especially from certain ethnic groups. Diagnosis is based on clinical assessment supported by investigations, including the finding of autoantibodies. Treatments range from antimalarial agents like hydroxychloroquine to corticosteroids and immunosuppressive agents. Despite advances in the treatment, patients with SLE often experience disease exacerbations (flares) of varying intensity followed by periods of remission. Their diagnosis is primarily made on clinical grounds after exclusion of other diseases or disturbances, primarily infections. Serological tests such as serum complement fractions and anti-dsDNA autoantibodies, are helpful in monitoring SLE activity. Flares are more frequent in patients with persistent immunological and clinical activity, and have been described as a significant risk factor for development of irreversible end-organ damage.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, relapsing, often febrile multisystem autoimmune disorder characterized by immune mediated tissue damage. The clinical
the spectrum of SLE is wide and ranges from benign easily treated disease with rash, arthritis, fatigue, to a very severe life-threatening illness with progressive irreversible damage. The course of the disease is variable and is characterized by flares of rampant inflammation that can threaten, in an unpredictable manner, almost any organ in the body, including the brain, kidney and heart. Therefore, flares can be considered as a reappearance of clinical features after remission, and then it becomes active again, either with new symptoms or a recurrence of old ones.
In 2011, Lupus Foundation of America defined a flare in a lupus patient as: "*a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment.*"[1]

The triggers for flare include:
1. Exposure to sunlight
2. Physical and mental stress
3. Intercurrent infections
4. Pregnancy
5. Non-compliance with treatment or sudden withdrawal of drugs.

Systemic Lupus Erythematosus Disease Activity Index (**SLEDAI**-Table 1) scores correlate with the clinician's impression of level of disease activity. An increase in SLEDAI > 3 indicates flare.

TABLE 1:

SLEDAI manifestation	Positive, % (*n* = 96)
Seizure	1
Visual	4
Cranial neuropathy	1
Lupus headache	1
Cerebrovascular insult	3
Vasculitis	14
Arthritis	24
Myositis	2
Cylinderuria	17
Haemoglobinuria	20
Proteinuria	23
Pyuria	0
Rash	34
Alopecia	8
Oral ulcers	4
Pleuritis	7
Pericarditis	5
Complement	45
Anti-DNA antibodies	33
Fever	11
Thrombocytopenia	6
Leucopenia	17
Other	0

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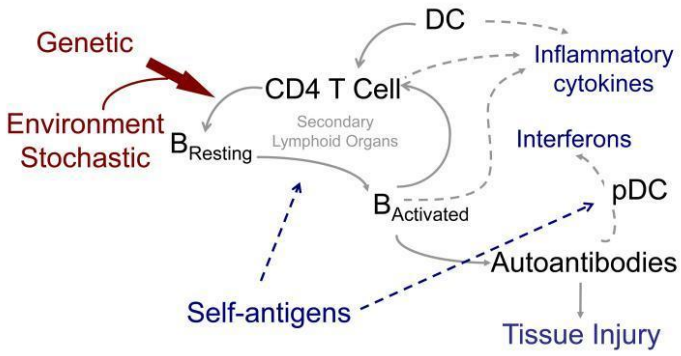
During flare, the organ system may be involved singly or in combination. The onset may be acute or insidious. The symptoms may be non-specific constitutional or specific for the organ
system involved. Arthralgia, fever and rash are the common presenting features.
Immunological profile in lupus flares includes high anti-dsDNA, high ESR, low complement (C3, C4, and *CH50*) levels and Anti-C1q antibodies, high titre of which is associated with lupus nephritis.

The **CLINICAL FEATURES** which can be considered as a warning of impending flare are:

- Increasing fatigue
- Arthralgias and myalgias
- New or worsening rash
- Persistent headache
- Fever
- Abdominal pain

PATHOGENESIS of lupus flare is characterized by global loss of self-tolerance with activation of autoreactive T and B cells leading to production of pathogenic autoantibodies and tissue injury[2]. Innate immune mechanisms are necessary for the aberrant adaptive immune responses in SLE.

Figure 1:



It is estimated that approximately 20–25% of SLE patients will flare within 1–2 years and 40–66% within 5–10 years after achievement of a low disease activity or remission status.[48] The most frequently involved organs are the mucocutaneous, musculoskeletal (arthritis), haematological, renal (30–40%) and immunology.

Several biomarkers have been evaluated as candidate tools for differentiation of SLE flares versus infections. *C-reactive protein* levels tend to rise significantly during active infections; whereas in the setting of a lupus relapse, elevation is usually mild or absent[3]. Serum *procalcitonin* (PCT) is another biomarker that increases in bacterial infections but remains low during viral infections and non-infectious inflammatory conditions, making it a potentially useful tool for distinguishing between serious infections and disease exacerbations in SLE[4]. Specifically, low serum PCT levels (<0.17 ng/ml) had >90% negative predictive value for ruling out bacterial infection in SLE patients[5].

Serum autoantibodies and complement factors are widely used for measuring activity and diagnosing flares in SLE[6]. Antibodies to double-stranded DNA (anti-dsDNA) are found in approximately 50% of SLE patients[7], and their serum levels correlate with lupus activity, especially nephritis[8]. Increases in anti-dsDNA frequently (40–60%) precede disease exacerbations by a period of few weeks or months, especially in the context of renal involvement[9]. Antibodies to complement 1q (anti-C1q) have also been described as indicators of disease activity, especially nephritis, in SLE[10]. Several studies have suggested a possible role of anti-C1q in early detection of renal relapse[11]. Various proteins of the complement pathway are linked to SLE pathogenesis and have been used to measure its activity. Serum C4 (but not C3) levels tend to decrease approximately two months prior to clinical appearance of a renal flare, reflecting the early activation of the classical complement pathway.

Patients with active ***lupus nephritis*** often have other symptoms of active SLE, including fatigue, fever, rash, arthritis, serositis, or CNS disease. These are more common with focal proliferative and diffuse proliferative lupus nephritis. Nephritis is characterized by peripheral edema secondary to hypertension or hypoalbuminemia. Extreme peripheral edema is common with diffuse proliferative or membranous lupus nephritis. During flare, the WHO histopathological class changes to a higher level with additional features of activity or chronicity. Basic hematological profile reveals anaemia, raised ESR and thrombocytosis. Urine examination will show proteinuria, leukocyturia, haematuria and casts. Complement levels fall and dsDNA levels rise. Renal biopsy should be considered for any patient with SLE who has clinical or laboratory evidence of active nephritis (active urinary sediments, RBCs, albuminuria with 24 hr urinary protein >500mg) especially with the first episode of nephritis. Renal biopsy may be useful in patients with recurrent episodes of nephritis, by revealing the histological pattern and stage of disease (activity and chronicity). It is also useful in determining prognosis and planning treatment.

From a clinical viewpoint, identifying SLE patients who are at greater risk to develop flares, especially severe flares, is important in designing and implementing preventive strategies.

Azathioprine has been compared against cyclosporine in active SLE requiring ≥15 mg prednisolone/day with comparable results in reduction of disease activity and prevention of flares[12]. In a randomized controlled study, patients with inactive disease who continued treatment with hydroxychloroquine had 74% lower risk for developing severe flares compared to their littermates who discontinued the drug[13]. A similar protective effect of hydroxychloroquine has been demonstrated in patients with stable lupus nephritis on maintenance treatment[14].

With regards to **lupus nephritis**, a controlled study in Caucasian patients with class III–IV lupus nephritis showed that maintenance treatment with azathioprine was as efficacious as mycophenolate mofetil in preventing renal flares and development of end-stage renal disease over a period of 10 years[15]. Conversely, in the racially mixed Aspreva Lupus Management Study, maintenance treatment with mycophenolate mofetil was associated with significantly fewer renal relapses compared to azathioprine over a period of 3 years[16]. Together, ***mycophenolate mofetil*** may be preferred as a maintenance regimen in patients with more severe (clinically or histologically) lupus nephritis.

CASE REPORT: We had a patient of 29 years old, married lady, mother of two, resident of West Bengal who was diagnosed with **Neuro-lupus** by us about a year ago. Back then she presented with fever, proximal myopathy, joint pain, skin rash, oral ulcer, abnormal behaviour followed by seizure. EEG revealed diffuse encephalopathic changes. MRI brain showed symmetrical bilateral cortical hyperintensity with restricted diffusion. NCV/EMG showed axonal neuropathy & myopathic pattern. CSF study done back then revealed cell count of 5 cells/ cu.mm, absent coagulum, glucose= 42 mg/dl, proteins= 69 gm/dl, Chloride 128 U/L, ADA= 3 U/L. Her ANA profile showed *ANA hep-2 positive* in 1:160 titre with high titres of *Anti ds DNA* and strong positive *Anti Ribosomal-P* suggestive of **Neuropsychiatric SLE**. After ruling out infections she received a pulse dose of IV Methylprednisolone followed by 6 cycles of cyclophosphamide. After that she was put on Azathioprine and corticosteroids for long term immunosuppression. She presented to us again a month back having some behavioural problem, cognitive decline, fever, intermittent headache, visual hallucination, depressed mood, reduced attention span and anxiety. She was hemodynamically stable. On further enquiry her family members informed that owing to financial problems during country wise lockdown for the pandemic, they were unable to continue her treatment with Azathioprine & steroids. Following non-compliance with the drugs she started having these problems. The investigation reports are as follows:

TABLE 2:

VARIABLES	RESULT
Hemoglobin	9.4 gm%
Total Leukocyte Count	3900 cells/cumm.
Platelet Count	1 lakhs/cumm.
CRP	36 mg/L.
ESR	64 mm in 1st hr.
RA factor	< 8 IU/ml.
Anti CCP	< 7 IU/ml.
Sodium	132 mEq/L
Potassium	3.8 mEq/L
Magnesium	1.8 mg/dl.
Calcium(corrected)	8.64 mg/dl.
Phosphate	3.0 mg/dl.
Vitamin B12	**338 pg/ml**
Vitamin D 25 OH	138 nmol/ml
Serum Procalcitonin	0.9 ng/ml
LDH	602 U/L
FBS	78 mg/dl
Urea	15 mg/dl
Creatinine	0.9 mg/dl
CPK	738 U/L
T. Protein	6.2
AST	46
ALT	43
ALP	154
C3, C4 levels	Low

ANA hep-2 (1:160)	**Positive**
SSA	**Positive**
Anti ds DNA	Strong Positive, high titre

She was diagnosed with **SLE flare**, more specifically ***CNS flare***. She was admitted and given Methylprednisolone 1 gm IV daily for 3 days followed by Azathioprine and oral corticosteroids to maintain immunosuppression. Antipsychotic & anxiolytic were also prescribed. She came for follow-up after a month and was better. Her cognition improved and she also participated in household chores.

DISCUSSION

Central Nervous System (CNS) flare includes *Headache* (24-72%)[17], *Psychosis (8%), mood disorder and anxiety*[18], General / focal *seizures* (6-51%), *Demyelination, transverse myelopathy, chorea* (Incidence is 1-3%), *Sensory motor neuropathy* (incidence up to 28%).
Important step is to determine whether the event can be convincingly attributed to SLE. Low haemoglobin, high ESR, low C3, C4 levels, rising titres of dsDNA indicate a flare. CSF study to rule out infections such as tuberculosis and India ink preparation for fungi is the next important step. Methylprednisolone 1 gm IV daily for 3 days followed by IV cyclophosphamide 1 gm on the 4th day is a standard protocol to initiate immune suppression. Oral corticosteroids 1 mg/kg are recommended as maintenance therapy along with 1 gm CYC monthly for 6 months and then 3 monthly for 8 cycles. Maintenance with azathioprine is recommended on completion of induction with CYC. Anticoagulation is indicated strongly for focal disease and such a therapy will be lifelong. Cognitive assessment and intervention are beneficial on a long term. Plasmapheresis is indicated in CNS manifestations secondary to thrombotic thrombocytopenia. IVIg is reserved in non-responders to standard protocol or terminally ill patients. Anticonvulsants, psychotropics and anxiolytics are given as per indication.

CONCLUSION

Despite advances in the treatment, a significant proportion of SLE patients is prone to manifest one or more disease exacerbations which incur significant burden and may impact adversely on long-term outcome. The risk is particularly higher in context of continuous, uncontrolled serological and clinical disease activity, especially from major organs. Apart from targeting low disease activity or remission, physicians looking after SLE patients should therefore consider strategies for preventing disease exacerbations, particularly maintaining effective immunosuppressive and biological therapies at well-tolerated doses and for adequate time periods. Abruptly stopping medications, especially corticosteroids, can also cause flares and should be avoided. The key to successful management is regular follow up allowing monitoring of symptoms, disease activities and treatment related adverse effects. For the future, we eagerly await the establishment of biomarkers capable to predict future flares with high accuracy, thus enabling the implementation of patient-tailored preventive strategies.

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