Case Report

Systemic lupus erythematosus with cardiorenal and neuropsychiatric involvement complicated by macrophage activation syndrome in a young female

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with highly variable presentations. Since no definitive diagnostic criteria exist, clinicians often rely on classification criteria to establish the diagnosis. A 22-year-old female presented to our hospital with a 2–3 month history of fever and weakness, along with breathlessness for 15 days. She had previously sought treatment at multiple peripheral centers, where only symptomatic therapy was provided, but no investigations were done till a few initial visits. At the time of presentation, clinical examination and investigations revealed neuropsychiatric symptoms, pancytopenia, pericardial effusion, renal involvement, and positive SLE serology. During hospitalization, she developed macrophage activation syndrome and multiorgan dysfunction. She was treated aggressively with high-dose corticosteroids, plasmapheresis, cyclophosphamide, dialysis, and mechanical ventilation. However, her condition rapidly deteriorated and progressed to a fatal outcome, which probably could have been prevented if the case had been investigated, diagnosed, and referred early. SLE flare is a highly fatal condition that can present abruptly. In view of this, prompt diagnosis and treatment of SLE is mandatory. Recommending specific diagnostic criteria and increasing awareness amongst the primary care physicians so that they also have a high index of suspicion for the condition in the presence of constitutional symptoms can reduce chances of missed diagnosis and reduce morbidity and mortality.

Key words: Immunosuppressive therapy, Lupus flare, Macrophage activation syndrome, Multisystem involvement, Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by the presence of antibodies against nuclear and cytoplasmic antigens [1]. It predominantly affects women of childbearing age, exhibits a waxing and waning disease course, and can involve virtually every organ of the body [2,3]. Risk factors include genetic susceptibility, hormonal influences, and environmental triggers such as ultraviolet exposure, infections, and certain drugs [4]. Its prevalence varies globally, being higher in African, Asian, and Hispanic populations [5]. In India, the estimated prevalence is 3–10/100,000 [6]. It is associated with significant morbidity and mortality. However, with early diagnosis and close follow-up, approximately 80–90% of patients with SLE may have a normal life expectancy [6]. Patients present with variable clinical features ranging from constitutional symptoms, mild joint and skin involvement to life-threatening kidney, hematologic, or central nervous system involvement. The variable presentations, along with the lack of pathognomonic features or tests, pose a diagnostic challenge for the clinician [7]. About 1–2 years of delay in diagnosis has been reported [8], attributing to social disparities, limited knowledge about the disease among primary care physicians, poor referral systems, and a marked rural-urban divide in access to rheumatology services [8,9]. In addition to this, the lack of properly defined diagnostic criteria is another major factor for the delay in diagnosis. In the absence of SLE diagnostic criteria, SLE classification criteria are often used by clinicians. The improved classification criteria developed by the European League against Rheumatism

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(EULAR) and the American College of Rheumatology (ACR) [10] represent the most advanced and precise criteria to date, but they also include antinuclear antibody (ANA) testing, which has a sensitivity of 99% but a specificity of only 19%.

We report a case of SLE that presented in flare and rapidly deteriorated to become fatal. An early diagnosis and a timely referral probably would have improved the outcome. Hence, this case highlights an urgent need to put proper diagnostic criteria for SLE in place, to make it easy to diagnose in peripheral centres, resulting in timely referral and management.

CASE REPORT

A 22-year-old female presented to the emergency department with a history of low-grade fever for 2–3 months and progressive breathlessness on exertion, generalized weakness, and fatigue for the past 15 days.

The patient was asymptomatic until three months prior, when she developed low-grade fever and body aches. She sought care at multiple clinics. Symptoms transiently improved every time to reappear after a few days. However, no treatment records of the first 2 months of the clinician's visits were available. Fifteen days before presentation, she was again admitted to a private hospital with a fever. Investigations revealed pancytopenia (Hemoglobin [Hb] 4.0 g/dL, white blood cells [WBC] 2100/cumm, platelets 83,000/cumm), mildly elevated C-reactive protein (CRP), and erythrocyte sedimentation rate. Serologies for dengue, malaria, enteric fever, procalcitonin, and blood and urine cultures were negative. Ultrasound showed mild hepatosplenomegaly, and chest X-ray revealed mild cardiomegaly. Bone marrow biopsy revealed hypocellular marrow with normocellular maturation and decreased megakaryocytes. She received a packed red cell transfusion and was referred to our hospital, a tertiary care centre, for further management.

On arrival, she was conscious and oriented, with pulse 102 bpm, blood pressure 90/60 mmHg, respiratory rate 22/min, temperature 99.9°F, and SpO_2 of 90% on room air. Physical examination revealed a thin-built woman with conjunctival pallor, multiple oral mucosal ulcers, and mild bilateral pitting edema. The oral mucosal lesions showed areas of erythema and crustations mixed with hyperpigmentation and scabbing (Fig. 1). Respiratory examination revealed bilateral basal crepitations. She also had one episode of generalized tonic-clonic seizure on the day of admission. She was admitted to the intensive care unit, received immediate symptomatic and supportive treatment, and investigations were sent.

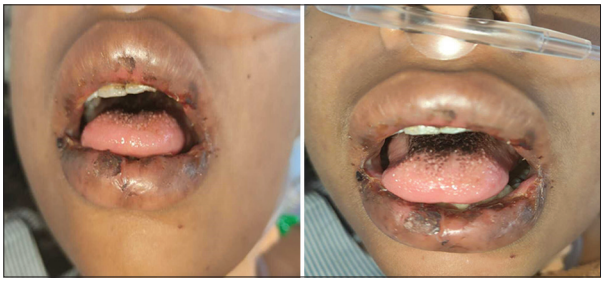

Figure 1: Oral and mucosal lesions

Initial laboratory investigations showed Hb 7.9 g/dL, WBC 3400/mm³, platelets 80,000/mm³, severe hyponatremia (Na^+ 112 mmol/L), hypoalbuminemia (1.5 g/dL), elevated liver enzymes (serum glutamic-oxaloacetic transaminase 410 U/L, serum glutamic-pyruvate transaminase 60 U/L, and alkaline phosphatise 216 U/L), normal bilirubin, urea 51 mg/dL, creatinine 0.5 mg/dL, and significant proteinuria (urine protein creatinine ratio [PCR] 4.53) with microscopic hematuria (Table 1).

Chest X-ray showed cardiomegaly with bilateral interstitial infiltrates and mild pleural effusion. Echocardiography revealed global left ventricular hypokinesia (ejection fraction 30%) with moderate pericardial effusion. Brain magnetic resonance imaging showed premature cerebral and cerebellar atrophy with early small vessel ischemic changes. Broad-spectrum antibiotics, anti-seizure therapy, hypertonic saline infusion, and IV albumin were added to the initial treatment. Given the chronic, multisystem nature of illness, autoimmune and infectious etiologies were considered. Viral serology (human immunodeficiency virus, hepatitis B surface antigen, hepatitis C virus) was negative. Immunological screening was positive for ANA. Anti-double-stranded DNA antibody, anti-nucleosome antibody, anti-Sm antibody, anti-RNP antibody, and Sm/RNP were all positive with mean values of 13±2.50 U/mL, 21±7.87 U/mL, 72±8.16 U/mL and 68±5.66 U/mL, and 80±8.89 U/mL. Both c-anti-neutrophil cytoplasmic antibody (c-ANCA) and p-ANCA were negative. Serum complement C3 and C4 levels were markedly decreased (<40 mg/dL and <8 mg/dL, respectively) (Table 1).

On scoring, it came out to be > 31 based on the 2019 EULAR/ACR classification criteria. A diagnosis of SLE was made. The activity score by SLEDAI 2K came out to be 17, indicating an active disease [11]. High-dose intravenous methylprednisolone (1 g/day) pulse therapy was started, along with hydroxychloroquine on day 3. Renal biopsy was planned after stabilisation.

On day 4, the patient's condition worsened with increased breathlessness, dropping oxygen saturation, hypotension, anuria, and focal seizures. She was put on a mechanical ventilator, inotropic support, and hemodialysis was initiated. Further workup revealed hyperferritinemia (>1500 ng/mL), hypertriglyceridemia (439 mg/dL), hypofibrinogenemia (<150 mg/dL), elevated lactate dehydrogenase (LDH) (1225 U/L), and worsening pancytopenia–consistent with macrophage activation syndrome (MAS) as per hemophagocytic lymphohistiocytosis (HLH) 2024 criteria [12]. Although infection and malignancy as causes of HLH were a possibility, age, elevated ferritin, and LDH did not favour the same.

Due to poor response to the treatment given, and in view of the critical condition and high probability of

Table 1: Serial laboratory investigations

Investigations	Range	Day 1	Day 3	Day 5	Day 10	Day 11	Day 15
Hemogram							
Hb (g/dL)	12–16	7.9	8.4	6.9	8.8	8.0	7.2
TLC (cells/µL)	4000–10000	3400	3100	3900	8500	12120	4600
Platelet count (cells/µL)	1.5–4 lakh	80000	68000	54000	84000	48000	21000
Renal function test							
BUN (mg/dL)	7–20	18	23	45	40	67	
Creatinine (mg/dL)	0.7–1.3	0.5	0.8	1.4	1.2	1.3	2.2
Liver function test							
T. Bilirubin (mg/dL)	0.1–1.2	0.8	1.0	0.8	0.5		1.0
Direct (mg/dL)		0.4	0.6	0.6	0.3		0.6
Indirect (mg/dL)		0.4	0.4	0.2	0.2		0.4
AST/SGOT (U/L)	10–40	410	260	218	77		124
ALT/SGPT (U/L)	7–56	60	39	42	25		65
ALP (U/L)	44–147	216	178	168	111		224
Sr. albumin (g/dL)	3.5–5.5	1.5	2.0	2.2	2.0		2.2
Sr. electrolytes							
Sodium (mmol/L)	135–145	112	126	130	134	133	136
Potassium (mmol/L	3.5–5.2	3.8	4.2	4.0	3.6	3.5	3.8
C-reactive protein	<1 mg/dL	9.86		22.8			52.6
ESR	0–20 mm/hr	35		34			
Urine routine							
Pus cells	0–5 HPF	2–3					
Protein	Negative or trace	3+					
RBCs	0–2 HPF	25–30					
UPCR	<0.2		4.53				
Ferritin				>1500			
LDH (U/L)	120–246			1225			
Fibrinogen (mg/dL)	200–400			<150			
Triglyceride (mg/dL)	<150			439			
Antinuclear antibody			Positive				
Serum C3 (mg/dL)	88–165		<40				
Serum C4 (mg/dL)	14–44		<8				
ANCA			Negative				

Hb: Hemoglobin, TLC: Total luecocyte count, BUN: Blood urea nitrogen, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvate transaminase, ALP: Alkaline phosphatise, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, UPCR: Urine protein creatinine ratio, LDH: Lactate dehydrogenase, ANCA-Anti-neutrophil cytoplasmic antibody, AST: aspartate transaminase, ALT: Alanine transaminase

fatal outcome, intensive immunosuppressive therapy (induction therapy) was needed to control the disease and halt tissue injury. Hence, plasmapheresis (PLEX) was commenced, combined with cyclophosphamide therapy. Steroid pulses were continued. Broad-spectrum antibiotic cover was also given to reduce the chances of associated infection. During PLEX and alternate-day hemodialysis, moderate clinical improvement was observed. The requirement of inotropic and ventilator support was reduced, with improved consciousness, increasing WBC and platelet counts, and seizure regression.

However, on day 11, the patient again developed high-grade fever. Repeat cultures were sent, and chest X-ray revealed new infiltrates. Multiple organ dysfunction syndrome worsened. Antibiotics were escalated, and a platelet transfusion was given. Despite aggressive multidisciplinary management, the clinical condition of the patient worsened, and she succumbed on day 15 of hospitalization.

DISCUSSION

SLE is a complex autoimmune disease with diverse clinical manifestations that may range from constitutional symptoms to multiorgan involvement [1]. Furthermore, there is no diagnostic criterion recommended as yet. Due to this, autoimmune causes of fever are often overlooked, and there is a delay in suspicion and diagnosis. This was a case of a young female who presented in the severe active stage of SLE, complicated by MAS after being symptomatically treated at various peripheral hospitals. Eventually, she developed multiorgan failure with a fatal outcome.

Pancytopenia and proteinuria observed on laboratory investigations suggested an underlying systemic inflammatory process, prompting evaluation for an autoimmune etiology in the absence of infection (negative procalcitonin and repeated sterile cultures) or malignancy (no malignant cells on bone marrow examination and no

radiological evidence). The presence of ANA positivity, together with anti-dsDNA and anti-Sm antibodies with low complement levels, established the diagnosis of SLE. Furthermore, the combination of pancytopenia, positive autoimmune markers, and pleural as well as pericardial effusions indicated severe, active disease [11].

Central nervous system involvement, shown by seizures, added to the evidence for the severity of the SLE flare. Hyponatremia was also present, which is an under-recognized feature of lupus flares, particularly when accompanied by neuropsychiatric symptoms like seizures, as seen in our patient [12,13]. It may result from syndrome of inappropriate antidiuretic hormone, renal involvement, or hypothalamic–pituitary axis dysfunction, all of which may occur in SLE patients [13]. The presence of significant proteinuria (urine PCR 4.53), microscopic hematuria, and low serum albumin raised the need for renal biopsy to diagnose and stage lupus nephritis, a common and serious manifestation of SLE that affects nearly 50% of patients during the course of illness [14]. However, a renal biopsy could not be performed due to rapid clinical deterioration and unstable hemodynamic conditions.

According to the 2019 update of the EULAR recommendations for the management of SLE, treatment of SLE-related neurologic disease should include glucocorticoids and immunosuppressive agents [15]. Hence, cyclophosphamide was administered besides glucocorticoids. The diagnosis of MAS was established based on persistent fever, worsening pancytopenia, hyperferritinemia, hypertriglyceridemia, elevated LDH, and hypofibrinogenemia [12]. MAS is a rare but often fatal complication of SLE, reflecting a hyperinflammatory state driven by uncontrolled immune activation [16]. It is more frequently seen in juvenile SLE but is increasingly being reported in adults, especially in patients with lupus nephritis and neuropsychiatric involvement [17]. Given the severity of this syndrome with high mortality reports, aggressive treatment is advised. Hence, despite the chances of infection, intensive immunosuppressant therapy was given with antimicrobial cover [18].

In cases refractory to steroids or complicated by MAS, additional immunomodulatory strategies are needed. PLEX has been shown to help by removing circulating immune complexes, autoantibodies, and pro-inflammatory cytokines, and is particularly useful in patients with life-threatening manifestations such as neuropsychiatric lupus, lupus nephritis with rapid progression, or MAS [19]. Studies and case series support the use of PLEX in combination with cyclophosphamide or rituximab in severe lupus cases unresponsive to standard therapies [19,20]. Hence, PLEX was initiated due to poor response to steroids and deteriorating neurological and hemodynamic status.

A similar case by Iftikhar *et al*. reported a 43-year-old woman who presented with status epilepticus refractory to conventional antiepileptic therapy and was later diagnosed with SLE based on persistent ANA positivity, arthritis, malar rash, and seizures. She was treated with intravenous methylprednisolone, followed by rituximab and oral prednisolone (45 mg), which was gradually tapered with subsequent clinical improvement [21]. Similarly, Faruk *et al*. described a 7-year-old girl admitted with seizures who was later diagnosed with SLE. She received intravenous pulse methylprednisolone followed by oral prednisolone, leading to normalization of C3 and C4 levels and resolution of symptoms [22].

Our patient presented with extensive multisystem involvement, including neuropsychiatric lupus, lupus nephritis, cardiac dysfunction, and cytopenias, all of which are recognized indicators of poor prognosis in SLE [23]. Despite aggressive treatment, the patient showed clinical deterioration and worsening organ involvement. She eventually developed refractory shock, requiring vasopressor (in the absence of evidence of infection or malignancy, this was attributed to cardiovascular dysfunction and HLH), and succumbed to the condition, resulting in a fatal outcome.

CONCLUSION

SLE remains a diagnostic challenge, especially in resource-limited settings and in the absence of universally accepted diagnostic criteria. This case of severe SLE with multiorgan involvement, complicated by MAS, represented a diagnostic and therapeutic challenge from the outset and throughout hospitalization, with progressive clinical deterioration despite aggressive treatment. It highlights the importance of early suspicion and thorough evaluation for autoimmune diseases in patients presenting with chronic fever and unexplained cytopenias. Being a high-mortality condition, timely diagnosis and a multidisciplinary approach remain the cornerstone for improving patient outcomes.

AUTHORS' CONTRIBUTION

Dr. Sona Mitra, Dr. Arti Muley: 1. Patient diagnosis and management. 2. Conception and data collection for case report. 3. Initial drafting of the case report and critical revision with final drafting. 4. Final draft approved.

Dr. Hardik Gajera, Dr. Priyal Patel, Dr. Vrushti Doshiyad, Dt. Hasmukh Chaudhary, Dr. Ritesh Patel: 1. Patient diagnosis and management. 2. Conception and data collection for case report. 3. Critical revision of initial draft and final drafting. 4. Final draft approved.

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