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Atypical Lupus Presentations and their Prognostic Implications

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Presented by

Yasmeen Abd EL-Fatah Mohamed Ahmed

Assistant lecturer of Physical Medicine, Rheumatology &Rehabilitation Department ,Faculty of Medicine, Sohag University

Supervised by

Prof /Ahmed Mohamed Mahrous

Professor of Physical medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Sohag University

Dr/Asmaa Khalifa Ahmed

Lecturer of Physical medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Sohag University

DR/Reham Alaa Eldin Hassan

Lecturer of Physical medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Sohag University

Sohag university

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- ## Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease that involve many different organs and display a variable clinical course.The prevalence of SLE varies across gender, race and geographic regions. SLE demonstrates a striking female predominance with a peak incidence of disease during the reproductive years[1].

The initial presentation of SLE is highly variable ranging from common mild symptoms to rare but severe organ involvement. Many patients first present with **typical features** such as musculoskeletal, mucocutaneous manifestations like photosensitivity or oral ulcers and constitutional symptoms including fatigue and fever. However a smaller subset of patients may initially present with **atypical or raremanifestations** such as neuropsychiatric symptoms, gastrointestinal , rare mucocutaneous, severe hematologic abnormalities, pulmonary hypertension or myocarditis[2].

Rare mucocutaneous manifestations of SLE include bullous lupus, lupus panniculitis and urticarial vasculitis. all occurring in a small minority of patients but often indicating more active or atypical disease[3].

Neuropsychiatric SLE (NPSLE) is a complex lupus manifestation with a broad range of symptoms from mild cognitive issues to severe central nervous system disease. Rarer symptoms like aseptic meningitis, movement disorders, myelopathy and demyelination can occur as initial presentations [4].

Chest involvement in SLE commonly includes pleuritis and pleural effusion. Less common but serious manifestations include pulmonary hypertension, shrinking lung syndrome, interstitial lung disease and alveolar hemorrhage may occur[5] .

Cardiac involvement is common in SLE affecting the pericardium, myocardium, valves, coronary arteries and conduction system. Pericarditis and premature coronary artery disease are most frequent. while myocarditis, pulmonary hypertension and Libman–Sacks endocarditis are less common[6].

Rare gastrointestinal involvement in SLE may include severe manifestations such as lupus enteritis (mesenteric vasculitis), protein-losing enteropathy (PLE), intestinal pseudo-obstruction or even intestinal necrosis[7].

Ocular involvement in SLE is well recognized but rare and vision-threatening manifestations including retinal vasculitis, vaso-occlusive retinopathy, optic neuritis and choroidopathy may also occur[8].

A minority of SLE patients present with severorgan-dominant disease that may not initially meet classification criteria making diagnosis challenging. Confirmation relies on excluding other causes and identifying highly specific SLE features such as SLE-specific autoantibodies or supportive histology. When these are absent, diagnosis is often delayed until more clinical or serological signs develop, which may worsen long-term outcomes[9].

Atypical age of SLE (late-onset SLE) is commonly defined as disease onset at or after 50 years of age and sometimes exhibits different clinical characteristics compared with the typical SLE phenotype. There is a higher proportion of male patients and a lower frequency of skin rash, renal involvement, neuropsychiatric manifestations, hypocomplementemiaand anti-DNA antibody seropositivitywhereas serositis is observed more frequently. Despite lower disease activity, it carries greater irreversible organ damage and a worse prognosis [10].

ANA has a high sensitivity, ranging from 95% to 97%, but a low specificity of 20%. High levels of ANA can be seen in several other disorders as well as a significant proportion of the healthy population; hence a positive ANA does not confirm the diagnosis of SLE but a negative ANA makes it less likely. Immunofluorescence assay (IF) is the gold standard test for ANA[11].

A small but well-documented subgroup presents with true ANA-negative SLE and diagnosis relies on other immunologic markers (anti-Ro/SSA, anti-Sm, low complement), histopathological findings and strong clinical suspicion. Thrombocytopenia, low complement, positive anti-dsDNA and medium-high titer aPL are the main manifestations of ANA-negative SLE [12].

Atypical presentations of SLE including unusual initial symptoms, predominant organ involvement, late-onset disease and ANA-negative remain poorly characterized. These forms are often associated with delayed diagnosis and potentially worse clinical outcomes. Most existing studies focus on isolated rare manifestations rather than analyzing atypical SLE as a cohesive category. Understanding these differences is crucial and this study aims to compare atypical and typical SLE presentations to clarify variations in prognosis, treatment requirements and subsequent organ involvement.

Aim of work:

To compare the prognosis of atypical versus typical SLE presentations, focusing on differences in disease activity, organ damage accrual, frequency of flares, diagnostic delay, treatment requirements and organ involvement during follow-up.

Patients and Methods:

- Type of the study: Prospective cohort study**.**

Patients:

The study will include 400 patients diagnosed according to SLICC classification criteria as systemic lupus erythematosus[13] including 3oo patients with typical common SLE presentation and 100 patients with atypical presentation as rare manifestations,ANA negative lupus, late onset lupus.Patients will be collected from Rheumatology outpatient clinic – Sohag University Hospital.

Inclusion Criteria

- **Patients diagnosed as SLE according to**SLICC 2012Classification Criteria[13] **:**

A. Patients presented with typical lupus presentation:

1. **age of onset (20-50)**
2. **common initial manifestations as constitutional manifestations,arthritis, mucocutaneousmanifestationslike malar rash, photosensitivity and hair falling.**

3. **patients with ANA positive.**

B. Patients presented with atypical lupus presentation:

1.any clinical presentation **not belonging to classic common SLE onset features**, including but not limited to:

- **Neuropsychiatric onset:** seizure, psychosis, aseptic meningitis, transverse myelitis
- **Cardiopulmonary onset:** pulmonary hypertension, acute pneumonitis, myocarditis, pulmonary hemorrhage
- **Gastrointestinal onset:** mesenteric vasculitis, intestinal pseudo obstruction, pancreatitis
- **Hematologic severe onset:** isolated severe thrombocytopenia, autoimmune hemolytic anemia, thrombotic microangiopathy
- **Dermatologic atypical onset:** bullous lupus, panniculitis, vasculitic ulcers
- **Myositis**
- **Fever of unknown origin (FUO)** as sole initial presentation
- Thrombotic events
- Generalized lymphadenopathy.

2. Patients with dominant organ affection.
3. **patients with late onset SLE.**
4. **patients with ANA negative SLE.**

C.Patients who can provide informed consent.

Exclusion criteria:

1. Patients whose initial symptoms are clearly attributable to infection, sepsis or another non-SLE condition.
2. Patients with chronic pre-existing diseases that may mimic or obscure the initial SLE presentation (e.g. primary epilepsy, primary pulmonary hypertension, chronic liver or GI disease).

3. Patients in whom onset features cannot be reliably classified as typical or atypical due to mixed or unclear presentation.

Methods of the study:

All patients will be subjected to the following:

Full medical history from the patients including Demographic data:(Age, sex,Disease duration, Time of diagnosis, Diabetes Mellitus, Hypertension), Clinical manifestations: categorize into typical (constitutional, mucocutaneous, musculoskeletal),atypical manifestations (Neuropsychiatricmanifestations,Chest,Cardiac and thrombotic event) and other manifestations and flare frequency throughout disease course.

Treatment that patients received: corticosteroids, immunosuppressive therapy eg, hydroxychloroquine, cyclophosphamide,mycophenolate mofetil, cyclosporine, Biological therapy.

Full general and rheumatological examination and assessment including:

Assessment of disease activity using SLEDAI-2k score

SLEDAI-2k is a validated and widely used global index that measures lupus activity over the preceding **10 days.** It includes clinical and laboratory domains including neurological, mucocutaneous, musculoskeletal, renal, hematological, serological, and constitutional manifestations. The total score ranges from **0 to 105**, with higher scores reflecting greater disease activity.[14]

Assessment of organ damage using SDI damage index:

The SDI measures cumulative, non-reversible damage that has been present for **at least 6months.** It includes**12 organ systems**: ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, endocrine,

malignancy and diabetes. The total score ranges from**0 to 47** with higher scores indicating greater cumulative organ damage.[15]

Laboratory investigation:

- Routine laboratory investigations (CBC, S.creatine, ALT, urine analysis, ESR, 24h urine protein or protein creatine ratio.)
- Immunological laboratory investigations:ANA (IF) ,anti dsDNA, anti-smith ,complements C3,C4)

Imaging or specific investigations related to affected systems:

- CT chest, MRI brain,Abdominal ultrasound,Doppler at UL,LL,ECG,Echocardiography
- Stage of lupus nephritis in case of renal affection

Ethical consideration:

This research will be revised by the Scientific Ethical Committee of Sohag University Hospital. An Informed written consent will be taken from all patients. A brief resume will be described to the study participants before inclusion in the study about the aim advantages and any hazards of the study.

Statistical analysis:

- Statistical analysis will be performed using the Statistical Package for Social Sciences (IBM-SPSS), version 24 (IBM, Chicago, USA).
- Data will be presented as mean, standard deviation (SD), number, and percentage. Mean and SD will be used for quantitative variables.
- Student's *t*-test will be used to compare means between two groups, while one-way analysis of variance (ANOVA) will be used for comparisons among more than two groups. The Mann–Whitney test will replace Student's *t*-test for non-parametric data.
- Pearson's Chi-square test will be used to compare qualitative variables; Fisher's exact test will be applied when expected frequencies indicate non-parametric distribution.
- Pearson correlation will assess relationships between two quantitative variables, whereas Spearman correlation will be used for non-parametric data.
- The level of statistical significance will be interpreted as follows:
    - **P > 0.05:** Not significant
    - **P < 0.05:** Significant

- **P < 0.001:** Highly significant

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