Preemptive SLE Diagnosis and Management

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Abstract

In this article we suggest that delay in Systemic Lupus Erythematosis (SLE) diagnosis and management is common because the symptoms often overlap with other diseases. We focus on SLE's early detection to avoid delay of management.

Some of the simple measures that can help achieve this goal include: the enhancement of general MSK examination skills and incorporating them in educational programs as clinicians do not exhibit enough trust in themselves when it comes to their examination skills.

We also hope to increase the awareness of the atypical presentations of SLE such as Immune Thrombocytopenic Purpura(ITP), Thrombotic Thrombocytopenia Purpura(TTP), Kikuchi-Fujimoto Disease(KFD)as well as Fever of Unknown Origin (FUO).

ITP is one of the major hematologic manifestations of SLE and can be the first presentation of the disease. Common findings associated with ITP include thrombocytopenia, petechiae and epistaxis. On the other hand, while TTP rarely presents as the initial manifestation of SLE, it denotes ongoing disease activity. Hence, general practitioners should be mindful of SLE as a possible diagnosis in the aforementioned presentations.

The nervous system, could be involved in this disease also with mood disorder and psychosis being two examples of said involvement.

Practitioners should also recognize late-onset SLE and consider it as the diagnosis in elderly patients who has some SLE manifestations.

The article also describes organs' involvement such as lupus nephritis. Its detection can be delayed as a result of not considering early kidney biopsy in the course of the disease.

Furthermore, one of these issues is negligence of coronary artery disease risk factors such as high blood pressure and high fasting blood glucose levels and not taking antimalarial drugs into account when treating SLE.

In conclusion, we introduce the obstacles in diagnosing and managing SLE patients both early and effectively specially when it comes to acutely ill patients.

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Preemptive SLE Diagnosis and Management

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by multi-system involvement with clinical exacerbation and multiple remissions. Its early detection is essential for its proper management. However, early diagnosis of the disease poses a difficult challenge for clinicians due to its various clinical manifestations which could be mixed up with other conditions. This often leads to a delay in the management of SLE. This results in not starting proper treatment early enough, leading to development of further irreversible complications related to SLE.

In this article we present our attempts to narrow down the issues that may cause such a delay by suggesting ways that can help timely management of SLE. To fulfill this aim, we stress on musculoskeletal (MSK) examination, describe atypical presentations of SLE, such as in the cases of Immune Thrombocytopenic pupura (ITP), Thrombotic Thrombocytopenia Purpura (TTP), Kikuchi-Fujimoto Disease (KFD), fever of unknown origins (FUO), and the nervous system involvement, recognize late-onset SLE, and describing organs' involvement such as kidney's involvement in SLE.

The article is divided into introduction, a part where we describe complications and a part where we discuss management issues and a conclusion.

Issues that may cause such a delay in diagnosis

I- Conducting an MSK Examination

Joints affection occurs in most of patients with SLE and is often one of the earliest manifestations of the disease. In fact, arthritis and arthralgias have been noted in up to 95 percent of patients with SLE (1). Yet, picking up MSK findings in patients with SLE is perplexing.

The classical presentation of arthritis in SLE patients is usually symmetrical and polyarticular with a predilection of knee, wrist, second and third metacarpophalangeal joints as well as interphalangial joints (1). However, the major difference between SLE and rheumatoid arthritis is that rheumatoid is characterized by joint deformities and erosions, while these are rare in SLE.

The other frequent MSK finding in SLE patients is myopathy, which can be inflammatory during the period of active disease or secondary after glucocorticoid steroid therapy.

Early detection of arthritis highly depends on MSK examination skills but there is a low level of competence and confidence among clinicians with them despite the high prevalence of MSK disorders in all fields of clinical practice (2)(3)(4).

As for arthritis, asking about morning stiffness, joints swelling and limitations in activities of daily living such as opening jars, tying shoes or buttoning shirts and performing simple active range of motion testing to assess function, joints palpation to look for tenderness and to detect any effusion are simple enough yet effective techniques that can empower the practitioner to diagnose arthritis and set management plans early so as to avoid risky situations later.

II- Atypical presentations of SLE

These are atypical presentations of SLE. Nonetheless, they are clinical presentations that should be known for primary health care physicians. Lack of knowledge of these clinical presentations causes a significant delay in establishing the diagnosis of SLE patients with a subsequent delay in the management of the disease.

- An association between **Immune Thrombocytopenic Purpura (ITP) and SLE** has been recognized for decades and it can be the first manifestation in some patients with SLE[5][6].It presents by symptoms related to decrease platelet count as petechial hemorrhage, easy bruising, gum bleeding or epistaxis and menorrhagia in women. It has been estimated that 3-15% of patients with isolated ITP develop SLE[7].

- SLE is one of the secondary causes of **Thrombotic Thrombocytopenia Purpura** (TTP) and it correlates with disease activity[8]but rarely occurs as a first manifestation although there was a reported case in which a patient was diagnosed to have TTP and SLE simultaneously[9].Such situations make the diagnosis of TTP in SLE patient difficult as classical TTP symptoms may be due to SLE disease activity. Therefore, it is important to consider SLE as a disease possibility.

- It has been recognized that there is a rare association between **SLE and Kikuchi-Fujimoto Disease (KFD),**alsocalled Necrotizing Lymphadenitis, which is a rare, benign and self-limited diseasethat mainly affects young women. Characterized by localized lymphadenopathy. KFD is found to be associated with many co-morbid diseases, of which SLE was the most frequently associated with. Among 224 cases with KFD 32 of these had SLE. Of them; eighteen (56%) had both diseases together, six (19%) developed SLE later, four (12%) already had SLE previously and four (12%) had incomplete SLE and they did not meet the American College of Rheumatology (ACR) criteria for SLE[10].

- **Fever of Unknown Origin** (FUO) remains a diagnostic challenge. The four main clinical categories of FUO are infectious, noninfectious inflammatory diseases, malignancy, and miscellaneous disorders. In one of the latest published article series on the subject, 73 patients from Netherlands seen between December 2003 and July 2005 were evaluated for FUO. The most common diagnosis was connective tissue diseases (22%), followed by infection (16%), malignancy (7%), miscellaneous (4%), whilst no diagnosis was reached in 51% of patients. Hence, clinicians must bear in mind the importance of ANA testing in such cases[11].

- **The nervous system might be involved in SLE causing various neurological and psychiatric symptoms** which are either diffuse or complex. Neurological and psychiatric symptoms are reported to occur in 10 to 80 percent of patients prior to the diagnosis of SLE or during the course of their illness[2]. Definitions of the 19 neuropsychiatric SLE syndromes, either central or peripheral, has been formulated by The American College of Rheumatology (ACR)[12] as in table(1) below:

Table(1): Neuropsychiatric manifestations of systemic lupus erythematous (SLE)

Central	Peripheral
Aseptic meningitis	Guillian-Barre syndrome
Cerebrovascular disease	Autonomic neuropathy
Demyelinating syndrome	Mononeuropathy
Headache	Myasthenia gravis
Movement disorder	Cranial neuropathy
Seizure disorder	Plexopathy
Myelopathy	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive disfunction	
Mood disorder	

Psychosis

III- Late onset SLE

SLE has always been considered a disease of the young but it can occur in the elderly, which is the type of SLE whose manifestations begin after the age of 50. Little attention has been given to this since the incidence of late-onset SLE is low ranging from 3.7%[13] to 20.1%[14].

We reported a case of late onset SLE in a 65 year old female patient, previously healthy, who presented with progressive paraplegia and sensory level at T4[15]. MRI showed extensive transverse myelitis (TM) involving the thoracic spine. ANA, anti-double stranded DNA antibodies (Anti ds DNA) and lupus anticoagulant were all positive. The diagnosis was delayed for a month after hospital admission and so was the treatment because SLE was not considered in the basic differential diagnosis of this patient. In similar cases, SLE should be considered as a differential diagnosis while dealing with suggestive presentations in the elderly population.

Clinicians should recognize this clinical entity by ordering Antinuclear Antibody (ANA) test to assure early SLE diagnosis and to avoid unnecessary delay in the management. However, ANA testing should be used only as a supportive evidence of this disease if there's a reasonable suspicion of SLE from either history, physical findings or the results of routine blood tests such as CBC. A positive ANA result in a patient who has minimal or no symptoms of SLE can be misleading or may lead to erroneous diagnosis or inappropriate therapy.

IV- Organ involvement in SLE such as Kidneys affection

Determining the stage of kidney disease has a significant impact on determining therapy response. Early diagnosis of SLE would minimize the time required to take a kidney biopsy once renal involvement is evident. Kidney biopsy can also be a very important tool in predicting long-term prognosis. It can determine the degree and severity of renal involvement through established histopathological guidelines. It should be performed as soon as clinical signs of renal involvement

are evident, such as abnormal urine analysis and/or reduced renal function in order to accelerate treatment decision and minimize the risk of irreversible renal damage[16].

Lupus nephritis (LN) patients must be maintained on Antimalarial drugs (AMD) such as hydroxycholoroquine (HCQ) in order to prevent major damage to the kidneys.

Management issues

Other considerations are:

- AMD should not be discontinued once the symptoms have subsided as this action could accelerate deterioration of renal function. AMD, has an important role in decreasing the disease activity and improving the lipid profile. Thus, it decreases the risk of atherosclerosis. It also lowers fasting blood glucose and inhibits platelet aggregation and adhesion[17].

- Focusing on immunosuppressive therapy like Mycophenolatemofetil and steroid alone in patients with SLE is not enough. Physicians should monitor patient's blood pressure, dyslipidemia and protienuria vigorously since they play a significant role in the progression of the disease.

- Unfortunately, many clinicians including rheumatologists tend to delay introducing Angiotensin converting enzyme inhibitors (ACEI) or Angiotensin receptors blockers (ARB), or they do not introduce them early on through the course of the disease because they tend to focus more on acute and dramatic presentations of SLE rather than monitoring risk factors.

- Coronary artery disease (CAD) risk factors -such as BP, diabetes, and dyslipidemia- should be monitored closely. In fact, ACEI have an end organ protection effect by its multiple leverages on hypertension and proteinuria as well as delaying the occurrence of renal complications. They are also associated with decreased risk of disease activity in patients with SLE. Bearing in mind that SLE patients are chronic steroid users, which make

them liable for hypertension, diabetes mellitus (DM), and coronary artery disease (CAD), which is considered as the leading cause of early mortality in SLE.

In table 2 below, we summarize the conditions relevant to SLE with pointers of how to manage them.

Table(2):Plans and actions to avoid delay in SLE diagnosis and management

Plan	Action
1. Consider SLE in the differential diagnosis of multi-systemic presentation.	• Order ANA test.
2. Assure screening for MSK abnormalities in all acutely ill patients.	• Ask about joint pain, swelling and morning stiffness. • Perform simple active range of motion test.
3. Be aware of neurological manifestations of SLE i.e. seizure, stroke, MG etc.	• Include ANA test in your work-up screening. • Educate clinicians taking care of neurological diseases about this.
4. Be aware of CAD risk factors in SLE patients.	• Lifestyle modification and weight reduction. • BP must be taken in every clinic visit. • Annual fasting blood glucose testing. • Statins for LDL>130 mg/dl.
5. Decreasing disease activity as well as decreasing the risk of atherosclerosis.	• Maintain all patients on HCQ.
6. Detecting late onset SLE.	• Order screening ANA as appropriate to the clinical presentation. • Educate clinicians about this.
7. Avoiding lupus nephritis.	• Early kidney biopsy. • Maintain SLE patients on AMD.

Conclusion

Delayed SLE diagnosis will lead obviously to management delay, which can be harmful to patients. Our aim is to focus on how to prevent the deferment of SLE

diagnosis and management. Some of the measures that can help us achieve this include: the enhancement of MSK examination skills among clinicians and incorporating it in the educational programs; increasing the awareness of the atypical SLE presentations like, TTP, ITP, KFD, as well as considering SLE as a possible diagnosis in cases of FUO and nervous system involvement. Moreover, we raised some issues that would hinder diagnosing and managing SLE patients early and effectively specially when it comes to acutely ill patients.

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