OPINION

Diagnostic criteria for systemic lupus erythematosus: has the time come?

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Abstract | Systemic lupus erythematosus (SLE) is a multiorgan disease with protean manifestations. Because SLE is uncommon and heterogeneous, its diagnosis can pose a considerable challenge, especially for clinicians with limited expertise of the disease. This is particularly true at the early stages of SLE, when an inadequate number of features to secure the diagnosis might be present, and for patients presenting with uncommon features, which can nonetheless be severe and require prompt treatment. Furthermore, the suboptimal performance of immunological testing in patients referred for possible SLE has been highlighted. As a result, SLE remains largely a clinical diagnosis that is made after excluding alternative diagnoses. Diagnostic criteria can expedite diagnosis and treatment, but are not available for SLE. Thus, SLE classification criteria are often used, but strict adherence to these criteria could delay diagnosis. Therefore, while eagerly awaiting diagnostic criteria for this disease, we propose interim potential solutions to facilitate its diagnosis.

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Introduction

Systemic lupus erythematosus (SLE) is a well-characterized, but extremely heterogeneous, clinical syndrome with protean manifestations. The lack of pathognomonic features or tests poses a considerable challenge in SLE diagnostics. Moreover, in some cases, only a few features are present at disease presentation, and these features can resemble other autoimmune, infectious or haematological diseases. Occasionally, SLE can first present with severe or critical disease, which requires prompt diagnosis often with inadequate serological or clinical data.[1]

In this article, we discuss the diagnosis of SLE in patients presenting with early or incomplete disease, or with overlapping or atypical features. SLE 'mimics' often puzzle clinicians and we provide a minimum work-up for their exclusion. We also review data on serological tests and novel biomarkers alleged to aid the diagnosis of SLE. Diagnostic criteria for nonspecialists are an unmet need in SLE, a vacuum currently filled in part by classification criteria. This fact has prompted us to steer the discussions by comparing old and new classification criteria, highlighting limitations in their application to diagnosis, and proposing interim solutions based on evidence and experience. We also discuss clinical diagnostic reasoning in SLE and common heuristic and cognitive diagnostic flaws.

Competing interests
The authors declare no competing interests.

Epidemiology

Epidemiological features are essential in establishing the pre-test probability of a disease. On the basis of worldwide data, in most SLE cases the onset of disease occurs between the ages of 16 and 50 years; 10–20% of patients present before age 16 years, and 8–15% after the age of 50 years.[2–4] A few studies have reported increasing trends in the incidence of SLE during the past few decades,[5] mainly owing to improved diagnosis of mild forms of the disease, although data from the year 2000 onwards suggest stabilized rates.[3,6–8] Estimated incidence rates in North America, South America and Europe range from 1 to 23 per 100,000 per year.[3,7]

Prevalence rates for adult SLE are estimated to be as high as 150 per 100,000 people in the USA; in Europe, prevalence rates typically range from 20 to 50 per 100,000 people, but rates as high as 112–207 per 100,000 people have been reported for Afro-Caribbean populations in Europe.[3,6,7] Women are affected on average 6–8 times more frequently than men.[3,6,7] Data from the USA have shown that African American and Hispanic individuals are affected much more frequently than white individuals, and have higher disease morbidity.[9–12] Among Medicaid-enrolled children in the USA, the prevalence of SLE in 2000–2004 was 9.7 per 100,000, with 84% of patients being female and 37% having renal involvement.[13] The average incidence rate of childhood SLE was 2.2 cases per 100,000 per year in this study, and the average incidence rate of lupus nephritis was 0.7 cases per 100,000 per year.[13]

Clinical presentations of SLE

Patients with SLE can present with a variety of manifestations, which are often not unique to SLE and can differ according to the age of onset (Table 1). Although the exclusion of more likely alternative diagnoses is a critical aspect of SLE diagnosis, little attention has been paid to providing guidance for clinicians. We attempt to address this deficit in Tables 2 and 3. Drug-induced SLE should be suspected in patients who do not have a diagnosis or history of SLE but develop a positive antinuclear antibody (ANA) result and at least one clinical feature of SLE after an appropriate duration of drug exposure.

Early versus established SLE

The frequencies with which various features of SLE are observed differ according to the stage of the disease.[14,15] Frequent features at disease onset are arthritis (which occurs in 52% of cases), haematological disorders (such as leukopenia in 23% of cases and thrombocytopenia in 17% of cases), malar rash (in 27% of cases), photosensitivity (in 23% of cases) and ANA positivity (in 23% of cases) (Table 1).[16] At diagnosis and follow-up, the most common features are a positive ANA test result (in 88% and 96% of cases, respectively), immunological disorders (in 60% and 90% of cases), arthritis (in 55% and 71% of cases), haematological disorders (in 54% and 70% of cases), malar rash (in 38% and 62% of cases) and photosensitivity (in

Table 1 | Frequency of manifestations at disease onset in adult versus childhood-onset SLE[14–16]

Frequency	Adult SLE	Childhood-onset SLE
Common manifestations (>30% of cases)	Arthritis and/or arthralgias Fever Photosensitivity Malar rash — —	Arthritis and/or arthralgias Malar rash Fever Photosensitivity Nephropathy Neurological involvement
Less common manifestations (10–30% of cases)	Leukocytopenia (lymphopenia) Raynaud phenomenon Serositis Nephropathy Neurological involvement Oral ulcers Alopecia Thrombocytopenia	Leukocytopenia (lymphopenia) Thrombocytopenia Serositis Raynaud phenomenon Oral ulcers Lymphadenopathy Alopecia —
Uncommon manifestations (<10% of cases)	Lymphadenopathy Discoid lesions Sicca syndrome Livedo reticularis Haemolytic anaemia Thrombosis Subacute cutaneous lupus Lung involvement Urticaria Purpura	Livedo reticularis Discoid lesions Haemolytic anaemia Thrombosis Sicca syndrome Subacute cutaneous lupus Lung involvement Urticaria Purpura —

Abbreviation: SLE, systemic lupus erythematosus.

34% and 52% of cases).[16] Thus, early on, cardinal features of SLE—such as malar rash, photosensitivity and ANA positivity—can be missing (or might be missed).

Does not look like SLE, but it is

ANA-negative SLE

Some patients might be diagnosed with SLE according to clinical intuition or the classification criteria (see Supplementary Table 1) even though they are ANA negative (titre <1:80 by immunofluorescence) at initial presentation or, rarely, throughout the course of the disease.[17] These patients should be managed similarly to ANA-positive patients with SLE.

Uncommon SLE manifestations

Patients presenting with infrequent or uncharacteristic SLE manifestations together with a paucity of common SLE features constitute a small but challenging group. A plethora of case reports and case series suggests that SLE might first present with fever, lymphadenopathy (simulating lymphoid or haematological malignancy), neurological events (such as seizures, cerebrovascular accident, encephalitis, myelitis, optic neuritis or chorea), unusual skin rashes (such as chronic urticaria or panniculitis), abdominal vasculitis, pneumonitis or pulmonary haemorrhage, pulmonary hypertension, isolated serositis, myocarditis, aplastic anaemia and isolated cytopenias.[14,15]

If atypical features are present, a rigorous search is required to rule out SLE-like genetic syndromes in children or immunodeficiency, infections or haematological diseases in adults. Enquiring whether the patient has experienced other manifestations of SLE in the past, and conducting a targeted examination together with serology testing, might help the clinician to reach a diagnosis in such cases. In our experience, non-rheumatologists often fail to recognize subtle evidence for the disease—such as faint or transient malar rash, mild arthritis or asymptomatic oral or nasal ulcers—or to elicit a history of photosensitivity, Raynaud phenomenon or other features of SLE that are not present at the time of the evaluation. Such symptoms are not usually volunteered by the patient unless specifically asked for. In other instances, this information, although retrieved, might not be integrated into the diagnostic thinking.

'Organ-dominant' SLE

Some patients might present with features affecting a single organ within the spectrum of SLE, in combination with SLE-associated autoantibodies, but with insufficient additional features to enable a diagnosis of SLE. Although in such patients the revised Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (see below) might enable the diagnosis of SLE in cases of lupus nephritis, they do not permit such a diagnosis for other organ manifestations. However, in clinical practice, patients with lupus rashes, recurrent pericarditis or pleurisy, thrombocytopenia, leukopenia or haemolytic anaemia, encephalitis or aseptic meningitis, demyelinating disease, optic neuritis or myelitis, together with relevant autoantibodies, might also qualify for a diagnosis of SLE after the exclusion of alternative diagnoses.

Looks like SLE, but it is not

UCTD

Some patients can present with a constellation of symptoms suggestive of SLE but do not qualify by clinical intuition or classification criteria as having the disease. These patients—who are often designated as having 'undifferentiated connective tissue disease' (UCTD) or 'incomplete lupus erythematosus'—usually present with one or two of the SLE classification criteria and other features suggestive of connective tissue disease, such as Raynaud phenomenon or constitutional symptoms. They account for 10–20% of referrals to tertiary care centres and might subsequently develop other diseases, such as systemic sclerosis, Sjögren's syndrome, mixed connective tissue disease (MCTD), rheumatoid arthritis (RA), systemic vasculitis, polymyositis or dermatomyositis. Only 10–15% fulfil the SLE classification criteria 5 years later. A distinct subgroup of patients with UCTD maintain an undefined profile during follow-up, with low disease activity, low frequency of flares and absence of severe organ involvement.[18] Prognostic factors for the development of SLE in patients with UCTD include malar rash, young age, alopecia, serositis, discoid lupus erythematosus, a positive Coombs test for haemolytic anaemia, hypocomplementemia, and a positive test for anti-Sm, anti-DNA or antiphospholipid antibodies.[19]

MCTD and rhupus

MCTD is characterized by overlapping features of SLE, systemic sclerosis and polymyositis or dermatomyositis, and by the presence of antibodies against the U1 small nuclear ribonucleoprotein. The existence of MCTD as a distinct clinical entity has often been debated, as in many patients the condition later evolves into another connective tissue disease.[20,21] Nevertheless, in a cohort of 161 patients with MCTD, more than half of the patients maintained their initial clinical and serological features and remained classified as having MCTD after an average

follow-up period of 7.8 years.[22] In addition, the term 'rhupus' is used to describe patients with overlapping features of both SLE and RA.[23] Arthritis is the predominant problem in these patients, and thus they are treated in a similar manner to patients with RA, with the exception that anti-TNF agents are not used, as these agents could potentially aggravate the SLE part of the condition.[24]

Diagnostic tests

ANAs

Although it is often stated that at least 95% of patients with SLE test positive for ANAs using immunofluorescence screening, the sensitivity of ANA testing can be as low as 70%, especially early in the disease.[25] This fact is particularly true in laboratories that use enzyme immunoassays or other automated assays, which display marked inter-manufacturer variation in performance and have a reported sensitivity of 70–98% for the detection of immunofluorescence-positive ANA titres ≥1:160.[26]

ANA screening also has a low specificity for SLE, which hinders its use for diagnosis. Indeed, considering the low prevalence of SLE, most individuals with ANA positivity do not in fact have SLE and have a low risk of developing the disease.

Anti-DNA antibodies

Antibodies against double-stranded DNA—which can be detected by the Farr assay, *Crithidia luciliae* immunofluorescence test (CLIFT) or ELISA—are found in up to 70% of patients with SLE at some point during the course of their disease and have 95% specificity in established SLE cohorts, making them a valuable diagnostic marker.[27,28] The prevalence of patients with SLE and a positive anti-DNA assay despite a negative ANA result has been reported to be 0–5.5%.[27,28] Early studies demonstrated that patients with UCTD who test positive for both ANAs and high-avidity anti-DNA antibodies (by Farr assay) are at increased risk of developing SLE within a few years.[29,30] However, a more recent study reported a low predictive value (46–61%) of anti-DNA antibodies (as measured by CLIFT) in unselected patients with recent onset of rheumatic symptoms.[28] Importantly, in this study, the risk of developing SLE or any other connective tissue disease within 5 years was not related to the CLIFT results.[28] Together, these data emphasize that anti-DNA antibody testing should be performed only when there is reasonable suspicion for underlying connective tissue disease or SLE in ANA-positive individuals.

Table 2 | A systematic approach to differential diagnosis in SLE*

Clinical presentation	Suggested work-up
Fever not suggestive of a self-limited disease (such as a viral infection)	CBC with differential WBC test, blood chemistry‡, ESR or CRP Urinalysis Blood and urine cultures (if urinalysis is abnormal) Imaging of the lungs or the abdomen (as indicated by symptoms)
Fever lasting ≥3 weeks	Testing for viral infections (hepatitis, CMV, EBV and HIV) and bacterial infections (Q-fever and brucellosis) Endocarditis work-up Abdominal imaging Lower extremity thrombosis work-up Rheumatoid arthritis immune work-up Giant cell arteritis work-up (in persons >65 years of age)
Acute confusion and/or meningoencephalitis	Neuroimaging studies CNS infection work-up
Cerebrovascular accident	Neuroimaging studies (including carotid artery ultrasound) Work-up for cardioembolic source Thrombophilia work-up
Myelopathy	Neuroimaging studies CNS infection work-up Demyelinating syndrome work-up Thrombophilia work-up
Seizure disorder	Neuroimaging studies EEG
Optic neuritis	Neuroimaging studies Demyelinating syndrome work-up Ischaemic optic neuropathy work-up Infections work-up (Lyme disease and syphilis serology) Vitamin B12 deficiency work-up
Serositis (pleural or pericardial effusion)	Infections work-up (including mycobacterial infection) Imaging studies
Cytopenia (anaemia, leukopenia, thrombocytopenia)	Exclude drug-associated causes Deficiencies work-up (for iron and vitamin deficiencies) Haematological disease work-up
Lymphadenopathy, splenomegaly and/or monocytosis	Haematological malignancy work-up Infection work-up (for viral infections, toxoplasmosis, leishmaniasis and malaria)
Haematuria and/or proteinuria	Renovascular imaging studies Renal disease immune work-up
Thrombocytopenia with microangiopathic haemolytic anaemia or with vascular thrombosis and skin necrosis	Haematological disease work-up Thrombophilia work-up Exclude drug-associated causes
Pneumonitis and/or pulmonary haemorrhage	Lung imaging and function studies Infection work-up (including bronchoscopy or bronchoalveolar lavage) Pulmonary disease immune work-up
Pulmonary hypertension	Lung imaging (of lung parenchyma and vasculature) and lung function studies Heart disease work-up (consider right heart catheterization)
Ischaemic abdominal pain§	Imaging studies Thrombophilia work-up
Chest pain	Heart disease work-up Pulmonary embolism work-up
Abnormal liver function tests	Imaging studies Viral hepatitis work-up Liver disease immune work-up

*Lupus serologies (ANAs, anti-ENA antibodies and complement component levels) should be assessed in all patients; specific tests should be conducted as indicated by clinical signs and symptoms, exposure history and/or abnormal laboratory tests. ‡Including LDH and liver function tests. §Severe, diffuse abdominal pain of sudden onset. Abbreviations: ANA, antinuclear antibody; CBC, complete blood cell count; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; EBV, Epstein–Barr virus; EEG, electroencephalogram; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; SLE, systemic lupus erythematosus; WBC, white blood cell.

Table 3 | Features at initial presentation not suggestive of idiopathic SLE

Feature	Alternative diagnosis
Recurrent infections, hypogammaglobulinaemia and autoimmune cytopenias	Immunodeficiency (complement deficiencies or common variable hypogammaglobulinaemia)
Familial SLE or very early childhood SLE	Complement deficiencies; genetic overproduction of interferon-α (for example, chilblain lupus erythematosus, which is linked to mutations in *TREX1*, *SAMHD1* and *ACP5* genes); apoptosis defects (linked to mutations in *DNASE1* and *DNASE1L3* genes)
Severe pancytopenia or neutropenia (absolute neutrophil count <500 cells/μl) or anaemia (haemoglobin <60 g/l) in the absence of haemolysis	Non-SLE-related acute haemophagocytic syndrome, leukaemia, lymphoma or myelodysplastic syndrome
Monoclonal expansions of B and T cells (as assessed by immunophenotyping), monocytosis or macrocytosis	Leukaemia, lymphoma or myelodysplastic syndrome
Microangiopathic haemolytic anaemia, thrombocytopenia, acute renal insufficiency, fluctuating neurological manifestations, fever, very low levels of ADAMTS13 (<10% of normal)	Thrombotic thrombocytopenic purpura
B (systemic) symptoms (high fevers with drenching night sweats and weight loss); marked splenomegaly, generalized lymphadenopathy or isolated lymphadenopathy with the lymph node >3 cm in diameter; or increased uric acid levels, hypercalcaemia, increased LDH levels and β2 microglobulin levels or the detection of monoclonal bands	Lymphoma
Prominent lymphadenopathy arthritis, Coombs-positive haemolytic anaemia, skin rash, fever and weight loss	Angioimmunoblastic T cell lymphoma or autoimmune lymphoproliferative syndrome
Exudative pleural effusion with high adenosine deaminase or interferon-γ levels, and low pH or low glucose levels	Tuberculosis reactivation or parapneumonic effusion
Relentless fever with severe, rapidly progressive cytopenias	Overwhelming infection, secondary haemophagocytic syndrome or acute leukaemia
Fever, arthralgias and/or arthritis and leukocytosis or high CRP levels	Infection, adult-onset Still's disease
Unilateral optic neuritis and pyramidal syndrome, with lesions detected by MRI suggesting dissemination in space (≥1 T2 lesions in at least two out of four multiple sclerosis-typical regions of the CNS [that is, the periventricular, juxtacortical, infratentorial and spinal cord regions]) or dissemination in time (simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time)	Multiple sclerosis
Longitudinally extensive myelitis with concurrent bilateral optic neuritis and anti-AQP4 antibodies	Neuromyelitis optica
Cerebrovascular accidents in the presence of multiple risk factors for atherosclerosis	Atherothrombotic disease

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with thrombospondin motifs 13; AQP4, aquaporin 4; CNS, central nervous system; CRP, C-reactive protein; LDH, lactate dehydrogenase; SLE, systemic lupus erythematosus.

Predictors of SLE

Individuals at risk of SLE include first-degree relatives of patients with SLE and patients with incomplete lupus erythematosus. In addition, some healthy individuals with positive ANA results (especially high positive) will subsequently develop SLE. Indeed, autoantibodies are typically present many years before the diagnosis of SLE and their appearance tends to follow a predictable course, with a progressive accumulation of specific autoantibodies while patients are still asymptomatic.[31] However, few quantitative or objective measures exist to establish risk of disease development in such individuals.

In a community-based cohort of >3,000 individuals, patients with incomplete lupus erythematosus had autoantibody profiles similar to those of patients with SLE, with the exception that they lacked antibodies specific for DNA and chromatin.[32] Some unaffected first-degree relatives had multiple autoantibody specificities despite an absence of clinical symptoms.[32] The population-based sample showed a 27% prevalence of ANA positivity, with high ANA levels (defined as >2 SDs above the mean) present in 2.5% of individuals.[32] At least one additional potentially pathogenic autoantibody was present in 1.7% of the population.[32] Individuals with the above-mentioned serological profiles might be at higher risk for subsequent development of clinical autoimmune disease, and most experts would agree that they should be monitored closely for the first 2 years.

Another study analysed the immunofluorescence patterns obtained during ANA testing.[33] A nuclear dense fine speckled pattern (resulting from autoantibodies that primarily target lens epithelium-derived growth factor) was observed only when testing serum from healthy ANA-positive individuals, whereas nuclear homogeneous, nuclear coarse speckled and nuclear centromeric patterns were identified only in tests from ANA-positive patients with autoimmune rheumatic diseases.[33] However, other patterns—including the nuclear fine speckled pattern, which was most common overall—were observed in both groups.[33] In our experience, the identification of ANA immunofluorescence patterns requires a dedicated laboratory and the prognostic significance of the results is rather limited.

Novel biomarkers

In addition to ANAs and anti-DNA antibodies, a number of other candidate biomarkers are being tested as diagnostic tools for SLE in general or for SLE with specific organ manifestations, but their utility in routine clinical practice has yet to be determined.[34] Furthermore, alternative approaches using new high-throughput technologies, such as transcriptomics and proteomics, have been applied. Upregulated genes observed in healthy individuals with high ANA levels who later develop SLE include some in the type I interferon signature (a pattern of gene expression observed in patients with SLE), suggesting that this signature could be a diagnostic biomarker.[35] Moreover, interferon-signature gene expression correlates with autoantibody profiles in patients with incomplete lupus erythematosus.[36] Patients with subacute cutaneous lupus,[37] discoid lupus[37] and immune thrombocytopenic purpura[38] have specific signatures that also include interferon-induced genes, suggesting common pathogenic mechanisms

and potentially explaining the transition to SLE that is observed at follow up in some patients with immune thrombocytopenic purpura.[38] In addition, serum type I interferon activity is high in patients with SLE and neuromyelitis optica but low in those with multiple sclerosis, suggesting similarities in pathophysiology between neuromyelitis optica and SLE but not across all autoimmune diseases.[39] Finally, RNA microarray analyses of peripheral blood leukocytes have been shown to distinguish between SLE flare and infection on the basis of differential patterns of expression of gene transcripts encoding interferon-inducible and plasma cell-associated genes.[40] These findings support the hypothesis that the type I interferon signature is involved in the pathogenesis and progression of SLE, and suggest that it might be useful in the diagnosis and monitoring of the disease. However, further studies would be required before it could be used in clinical practice.

Proteomic analyses in SLE have revealed autoantibodies against skin antigens,[35] as well as differences in the predominant isotype of autoantibodies between incomplete lupus erythematosus (in which IgM predominates) and established SLE (in which IgG predominates).[41] Whether incomplete lupus erythematosus represents an early stage in the development of SLE, before class switching to IgG, or whether the predominance of IgM autoantibodies is persistent and relatively protective is not known. Silverman *et al.*[42] applied proteome multiplex microarray technology using control ligands and 65 autoantigens (including a diverse range of nuclear and cytoplasmic molecules) recognized by disease-associated and natural autoantibodies. Longitudinal analyses of unrelated patients with SLE showed that autoantibody profile patterns are patient specific and highly stable over time. In addition, shared IgG autoantibody profiles were observed in monozygotic twins, suggesting that SLE-associated IgG autoantibodies can arise in predisposed individuals in genetically determined patterns.[42] If confirmed in larger studies, these results suggest that autoantigen microarrays could be used to identify characteristic autoantibody fingerprints and facilitate SLE diagnosis.[42]

Clinical diagnostic reasoning

In SLE, as in other diseases, diagnosis is reached either by immediate recognition (which would occur, for example, if a young woman presented with a malar or discoid skin rash and polyarthritis) or by forming a hypothesis based on available data and proceeding in the diagnostic plan in a process known as probabilistic reasoning, which is based on a Bayesian approach. In simple terms, the likelihood of an SLE diagnosis in a patient with a certain feature is increased if this feature is commonly found in SLE and if SLE is prevalent in the patient's population demographic. For example, as SLE is ten times less common than autoimmune thyroid disease, a positive ANA test in a young woman with arthralgias—but not frank arthritis—is more likely to be due to the latter rather than the former disease. Similarly, SLE is unlikely if a certain feature that is highly frequent in the disease (such as ANA positivity) is absent and if the disease has a low prevalence in the patient's population demographic (for example, in young men).

Probabilistic reasoning involves four main steps.[43] First, the *a priori* probability of the disease is estimated based on the patient's demographics and clinical presentation. Considering the common family segregation of the disease,[44] the identification of first-degree relatives with SLE—either by examination or by history—might increase the odds of SLE in the patient. Second, the frequencies of features associated with a rigorously defined (gold-standard) disease entity (conditional probabilities) are determined. Clinical features with high diagnostic value for SLE include oral ulcers, alopecia, serositis, haemolytic anaemia, leukopenia, thrombocytopenia and neurological manifestations (see Supplementary Table 2). Third, the sensitivity, specificity, and positive and negative likelihood ratios (LRs) of the diagnostic tests are estimated. The LR is the likelihood that a given test result would be expected in a patient with the disease in question compared to the likelihood that the same result would be expected in a patient without the disease. Positive LRs >10 are considered to be very useful for diagnosis, those in the range 2–10 are considered useful and those <2 least useful. Negative LRs <0.1 are considered to be very useful for excluding a diagnosis, those in the range 0.1–0.5 are considered useful and those >0.5 least useful.[43] The last step is the setting of diagnostic thresholds. For example, if the pretest probability is low and a test is negative (as in the case of negative ANA test in a patient with arthralgias but no synovitis), then SLE can be excluded as a diagnosis.

Using probabilistic reasoning and Fagan's normogram (see Supplementary Table 2 and Supplementary Figure 1), and assuming a prevalence of SLE of 1% in a tertiary referral clinic, the post-test probability of a positive ANA result in a young woman with malar rash, arthritis and oral ulcers is >40%. If the same patient also tests positive for anti-DNA antibodies, the probability of SLE is >95%, whereas the probability of SLE in a young man with arthralgias, oral ulcers and a positive ANA result is < 1%.

An issue with relying on conditional probabilities is that this approach weights diagnosis against rare presentations, which are nevertheless common in SLE. In terms of clinical reasoning flaws, all types of heuristic and cognitive diagnostic flaws and biases may plague the diagnosis of SLE;[45] definitions and typical examples are shown in Supplementary Table 3. Nonetheless, until more data are available for the diagnostic value of symptoms, signs and laboratory findings, most experts would agree that a combined approach using empirical clinical judgement and conditional probabilities is most helpful in diagnosing the majority of SLE cases.

Classification criteria for SLE

The creation of diagnostic criteria for a disease as heterogeneous as SLE is a difficult task from which academics have shied away to date, in the hope that new molecular or serological tests will make it easier. As a result, the diagnosis of SLE has instead relied on the adaptation of classification criteria in the clinical diagnosis.

The ACR criteria

Criteria for SLE classification were developed by the American College of Rheumatology (ACR) in 1971, and revised in 1982[46] and 1997[47] to ensure that patients with SLE in clinical trials do in fact have a similar disease (see Supplementary Table 1). These criteria are not weighted for specificity, sensitivity or disease severity, and might exclude patients with early or limited disease. In fact, data from tertiary centres suggest that only 60% of patients referred for SLE fulfil the ACR criteria, whereas another 15% of patients have SLE features but do not fulfil the criteria.[48] Additional concerns regarding these criteria include the possible duplication of highly correlated cutaneous features (such as malar rash and photosensitivity) and the lack of inclusion of other cutaneous manifestations (such as maculopapular or polycyclic rash) and neurological manifestations (such as myelitis). In addition, the ACR criteria do not include low serum levels of complement components, and some experts are concerned

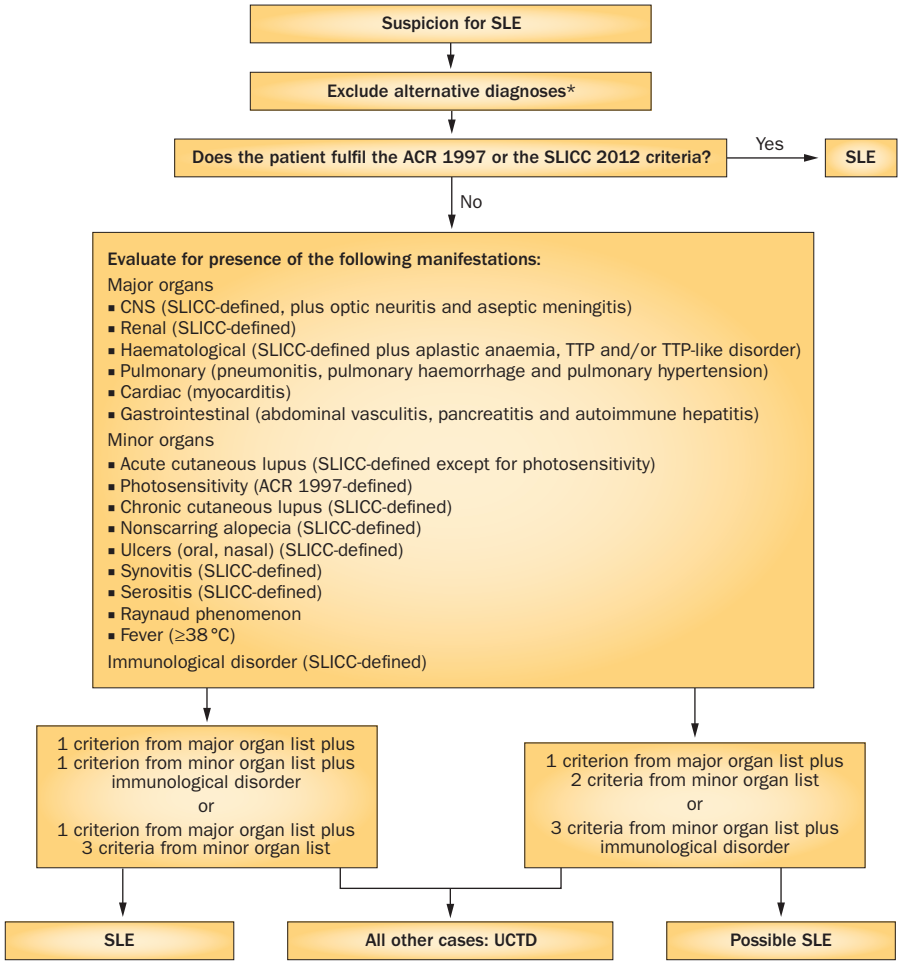

Figure 1 | Diagnostic steps in patients presenting with features suggestive of SLE. Patients diagnosed with 'possible SLE' should be managed similarly to patients with SLE and treated according to their symptoms and manifestations. If negative at baseline, immunological tests can be repeated at subsequent time points. *See Tables 2 and 3 for a systematic approach to excluding alternative diagnoses. Abbreviations: ACR, American College of Rheumatology; CNS, central nervous system; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics; TTP, thrombotic thrombocytopenic purpura; UCTD, undifferentiated connective tissue disease.

about patients without any immunological criteria being classified as having SLE, an autoantibody-mediated disease.

The SLICC criteria

The SLE classification criteria proposed by the SLICC in 2012 can be fulfilled in two ways: by biopsy-proven lupus nephritis in the presence of ANAs or anti-DNA antibodies as a 'stand-alone' criterion; or by meeting at least four out of seventeen criteria (including at least one clinical criterion and one immunological criterion) (see Supplementary Table 1).[49] The requirement for at least one immunological criterion was selected because SLE is considered to be an autoantibody-driven disease. The SLICC classification criteria have split the individual autoantibody specificities of the ACR immunological criterion into separate criteria, so that each might contribute to disease classification. The anti-DNA antibody criterion, however, requires a stricter cutoff for ELISA assays than that listed in the ACR criteria, and the antiphospholipid antibody criterion includes anti-β2 glycoprotein I antibodies. Although it did not improve the statistical modelling, low complement levels (based on C3, C4 or total haemolytic complement levels) were included as a criterion because of the involvement of complement in disease pathogenesis. The direct Coombs (antiglobulin) test was also included, but it is not counted if the patient has the clinical criterion of haemolytic anaemia.

In the derivation set, the SLICC classification criteria resulted in fewer misclassifications than the ACR classification criteria (49 versus 70 out of 702 patient scenarios), had greater sensitivity (94% versus 86%) and comparable specificity (92% versus 93%). In the validation set, the SLICC criteria resulted in fewer misclassifications (62 versus 74 out of 690 patient scenarios), had greater sensitivity (97% versus 83%) but less specificity (84% versus 96%).[49]

In summary, the SLICC classification criteria perform better than the revised ACR criteria in terms of sensitivity, but not specificity. These criteria are meant to be clinically more relevant, enabling the inclusion of more patients with clinically defined SLE into clinical trials and longitudinal observational studies. A significant advantage of the SLICC classification criteria is the inclusion of additional clinical and laboratory features without compromising the specificity. As with the ACR criteria, the SLICC criteria have not been tested for the purposes of diagnosis. Rather, their goal is to distinguish SLE from other rheumatic diseases. To this end, common features denoting a collagen vascular disease such as Raynaud phenomenon have been left out, whereas photosensitivity—a distinct feature of SLE—has been combined with rash, which might lead to a delay in diagnosis. Finally, other major organ manifestations (namely myocarditis, pneumonitis, pulmonary haemorrhage, aseptic meningitis, Libman–Sacks endocarditis and chorea), although not common, were left out; these features, although rare, might provide helpful hints in the diagnosis of SLE.

Which criteria enable early diagnosis?

In a study by Alarcon *et al.*,[50] patients with SLE were grouped according to whether the SLICC criteria were met before, at the same time as, or after the ACR criteria, and the groups were then compared. Out of 640 patients, 319 (50%) were classified at the same time using either criteria set, 78 (12%) were classified earlier using the SLICC criteria (average time-lag 0.7 years) and 225 (35%) were classified later using the SLICC criteria (average time-lag 4.4 years). Only 5 of the 78 patients who were diagnosed earlier using the SLICC criteria had lupus nephritis plus one immunological criterion. Of the patients diagnosed later using the SLICC criteria, in the majority of cases the delay was due to the combination of malar rash and photosensitivity into the acute cutaneous SLE criterion. Thus, despite their improved sensitivity compared with the ACR criteria, the SLICC criteria might delay the diagnosis of SLE in a substantial

number of patients, and some patients might not be classified at all. Therefore, combining malar rash with photosensitivity might not be as beneficial as initially thought, at least for diagnostic purposes. Importantly, the SLICC criteria were developed in referral centres and whether they can be generalized to other clinical settings remains to be seen.

Using classification criteria for diagnosis

Caveats exist in the application of either set of criteria for diagnosis in patients with early disease. Some systems are overrepresented in the criteria, and for the most part all features (with the exception of biopsy-proven nephritis in the SLICC criteria) contribute equally to classification, without any weighting based on sensitivity or specificity for each individual criterion. Some patients, including patients with major organ involvement, can have SLE disease manifestations for years before fulfilling the classification criteria. Importantly, the diagnostic utility of some tests or features of the disease might be reduced when applied to patients presenting to primary care centres with vague complaints resembling connective tissue disease. In our experience, an important clinical problem that diagnostic criteria would help to address is the diagnosis of patients with major organ involvement who are seen by clinicians who are not experts in SLE, as substantial delays in the initiation of treatment in such patients owing to strict adherence to classification criteria could have an effect on outcome. For such cases, we propose an approach that takes into consideration the strengths of both classification systems and incorporates common sense and clinical experience; these diagnostic guidelines are presented in Figure 1.

Conclusions and perspective

SLE remains largely a clinical diagnosis. In individuals with typical features of SLE but low-positive or negative ANA results, the clinician should not hesitate to establish the diagnosis of SLE after excluding other diseases. However, a considerable number of patients with features suggestive of SLE might never develop the disease. In such cases, we recommend the use of the term UCTD and the provision of a follow-up period of 2–5 years. These patients should be reassured that their prognosis is excellent. Our awareness of the unmet need for diagnostic criteria in SLE has prompted us to propose interim solutions based on evidence and our experience. We are aware that not everyone might agree with our approach. We eagerly await alternative viewpoints towards the common goal of improving diagnostics in SLE and facilitating earlier recognition and treatment. Notwithstanding the limitations of existing diagnostic features and tests, we believe that the time has come to introduce diagnostic criteria for SLE and further refine them as more experience accumulates.

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