RHEUMATOLOGY

Rheumatology 2020;59:v4–v11
doi:10.1093/rheumatology/keaa379

Classifying and diagnosing systemic lupus erythematosus in the 21st century

Martin Aringer [1] **and Sindhu R. Johnson**[2,3]

Abstract

The EULAR/ACR 2019 classification criteria for SLE constitute a current and optimized clinical approach to SLE classification. Classification is still not based on molecular approaches and the results from large studies using polyomics may be interpreted as demonstrating the relevance of the genetic and environmental background rather than splitting SLE into several entities. In fact, an association study within the EULAR/ACR classification criteria project found associations between manifestations only within organ domains. This independency of various organ manifestations argues for SLE as one disease entity. The current review article will therefore concentrate on the clinical and immunological manifestations of SLE and on what we have already learned in this century. Moreover, the structure and essential rules of the EULAR/ACR 2019 classification criteria will be discussed. While classification and diagnosis are distinct concepts, which have to remain clearly separated, information derived from the process towards the classification criteria is also useful for diagnostic purposes. Therefore this article also tries to delineate what classification can teach us for diagnosis, covering a wide variety of SLE manifestations.

Key words: systemic lupus erythematosus, classification, diagnosis, autoantibodies, nephritis

Rheumatology Key messages

- Positive ANA is required for SLE classification and ANA remains an appropriate screening test.
- While SLE manifestations are extremely variable, the 24 items in 10 domains will classify most patients.
- For classification and diagnosis, symptoms should only count when there is no more likely alternative explanation.

SUPPLEMENT

Introduction

With the new 2019 EULAR/ACR classification criteria for SLE [1, 2] and the classification criteria from the Systemic Lupus International Collaborating Clinics group published 7 years earlier [3], the 21st century has seen two large group efforts towards better criteria. While clearly advancing the field in a stepwise fashion, these criteria are strictly clinical. This has caused some disappointment, given that large polyomics approaches to better define autoimmune diseases have likewise been ongoing in the last decade. However, these have not yet led to a new understanding of SLE as a disease entity. Rather than seeing them as an indication that SLE consists of three different disease entities, we would interpret the available results as showing the impact of the (presumably mostly genetic) background on one variable systemic autoimmune and immune complex disease. We base this interpretation on clinical data of the EULAR/ACR project that show SLE manifestations largely independent of each other, with the exception of organ domains [4].

We will start with what we think we have learned about classifying in the first 20 years of this 21st century and then try to investigate potential applicability for SLE diagnosis. At the same time, we maintain that the two concepts of classification and diagnosis are separate. Classification is a scientific approach that uses a positive definition based on a limited number of items and aims at combining relatively homogeneous groups of

[1]Division of Rheumatology, Department of Medicine III, University Medical Center and Faculty of Medicine Carl Gustav Carus, Technical University of Dresden, Dresden, Germany, [2]Division of Rheumatology, Department of Medicine, Toronto Western Hospital, Mount Sinai Hospital and [3]Clinical Epidemiology & Health Care Research, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Submitted 3 April 2020; accepted 1 June 2020

Correspondence to: Martin Aringer, Division of Rheumatology, Department of Medicine III, University Medical Center and Faculty of Medicine Carl Gustav Carus, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany. E-mail: martin.aringer@uniklinikum-dresden.de

patients with a given disease. Diagnosis, in contrast, is a highly individualized approach concerning only one patient that can include all available information, is often iterative and heavily relies on the exclusion of other entities. Diagnosis is essentially always provisional, while classification is more specific and should therefore not be erroneous too often. In scientific terms, specificity is key for classification, while sensitivity is more important in diagnosis [5, 6], where a patient not diagnosed will usually not be treated. For these reasons, classification criteria should not be abused for making a diagnosis, even though diagnosis and classification will often concur.

Autoantibodies

In essence, SLE is a multi-autoantibody and immune complex disease [7, 8]. With more autoantibody tests available over time, immunological abnormalities are seen in essentially all patients with SLE. In parallel, the importance of securing the presence of immunological abnormalities has become obvious, with the phase II belimumab clinical trial showing effects in serologically active patients only [9]. While the latter is not surprising, the SLICC criteria have responded by making at least one immunological criterion an absolute requirement for SLE classification [3].

A systematic literature search and metaregression within the EULAR/ACR 2019 criteria project found that the vast majority of SLE patients [97.8% (95% CI 96.8, 98.5)] have positive ANAs, or have at least been ANA positive historically [10]. In a Delphi exercise, SLE experts all over the world also closely linked ANA and SLE [11]. Given the high sensitivity of the ANA test, combined with its low specificity, and the fact that ANAs are used as a screening parameter in clinical routines, ANAs are now an obligatory entry criterion for the EULAR/ACR 2019 SLE classification criteria [1, 2]. While this precludes (always) ANA-negative SLE patients from classification by the new criteria, this is a very uncommon situation acceptable for classification.

For diagnosis, it is important to stress that the sensitivity of ANA of 96–99% means that truly and persistently ANA-negative SLE is possible, although uncommon. Moreover, there are disquieting data that ANA sensitivity may be seriously deficient on some HEp-2 or HEp-2000 cell substrates, even when a highly experienced laboratory performed the IIF assay as the gold standard [12]. The same may be even more troublesome for other test systems, and it is important to know the true performance characteristics of the ANA test in local use. With an appropriately sensitive ANA test, however, an uncommon disease will be quite unlikely with the ANA screening test being negative.

Positive ANAs in SLE are mostly caused by antibodies to chromatin components, i.e. dsDNA and histone proteins that together form nucleosomes, and by RNA binding proteins, which are usually also found in the cytoplasm. Of the antibodies against RNA binding proteins, those against the Smith (Sm) antigen are specific for SLE, while isolated anti-U1RNP antibodies are the hallmark antibody of MCTD and anti-Ro and anti-La antibodies are even more common in SS and may occur in SSc. Accordingly, anti-Sm antibodies are included in the 1982 [13] and 1997 [14] ACR classification criteria, the 2012 SLICC criteria [3] and now the EULAR/ACR 2019 criteria [1, 2], where they have a weight of 6, more than half of the necessary 10 points needed for the classification cut-off.

The same is true for anti-dsDNA autoantibodies. However, for anti-dsDNA there are also significant test issues. As compared with the traditional *Crithidia luciliae* immunofluorescence test and Farr assay or RIA, which are highly specific, many of the other test systems lack this specificity. For the EULAR/ACR classification criteria, this led to the definition that anti-dsDNA antibodies count only if from a test system with a demonstrated specificity of at least 90% against relevant disease controls [1, 2].

For classification purposes, anti-Ro, anti-La and anti-U1RNP were not specific enough for SLE to include them [15], but they are useful for diagnostic purposes and routine tests give reliable results. For anti-histone and anti-nucleosome/anti-chromatin antibodies, the proven specificities for SLE were likewise not high enough for classification, but these antibodies still support an SLE diagnosis, as do anti-C1q antibodies, which are more closely associated with LN. In contrast, antibodies to ribosomal P are relatively specific, but often associated with anti-dsDNA [16]. The presence of multiple, non-related autoantibodies is an argument for the diagnosis of SLE. This concept was also evaluated for the EULAR/ACR criteria [17, 18] but could not be transformed to a single criterion that would not have been redundant with individual autoantibodies already included (i.e. anti-Sm, anti-dsDNA and aPL antibodies.

As false-positive syphilis serology, aPL antibodies have already been depicted in the 1982 ACR criteria [13], when the aPL concept [19, 20] had not yet been established. The 1997 revision already contained aCL antibodies and the lupus anticoagulant [14], and the SLICC criteria added anti-β2-glycoprotein I antibodies [3]. The latter three were retained for the EULAR/ACR criteria [1, 2], but have a relatively low weight of 2, since they are the hallmark of APS, which in about half of the cases is a distinct entity (primary APS) independent of SLE. Importantly, there are two distinctions between the definitions for APS [21] and SLE [1, 2]. In APS, two tests with a minimum time lapsed of 12 weeks are necessary in order to exclude short-term (IgM) antibodies following a vascular event or an infection [21]. For the SLE classification, aPL antibodies, like all other criteria, need only be present once [1–3]. On the other hand, IgA aPL antibodies, which as isolated antibodies play a minor role in APS and are therefore not an APS criterion [21], are common in SLE and therefore count for the SLE classification criteria [1–3].

Complement

SLE is an immune complex disease, and immune complexes activate complement and thus decrease serum protein levels [7]. In the absence of diminished production (e.g. in liver disease), diminished complement levels argue for immune complex deposition, which is not SLE specific. Nevertheless, measurement of serum C3 and C4 is an important test for monitoring SLE patients [22], with a decrease in both of these proteins mostly reflective of active immune complex disease, while genetic C4 deficiency is known to be a genetic risk factor for SLE [7, 23]. Low complement (C3 or C4 or CH50) was introduced into the SLICC 2012 criteria [3]. In the EULAR/ACR criteria, the combination of both low C3 and low C4 has a weight of 4, while either of the two has a weight of 3 points [1, 2]. Haemolytic complement measurement (CH50) is not routinely performed in many places today, and the tests for complement split products on other blood cells, mostly erythrocytes, are not yet standardized worldwide, but both would be considered in diagnosing SLE.

Mucocutaneous SLE manifestations

Skin manifestations are often important clues that facilitate an SLE diagnosis. The three main categories of SLE-specific manifestations are acute cutaneous LE (acLE), encompassing the malar rash and a generalized maculopapular rash, subacute cutaneous LE (scLE), with its annular or psoriasiform eruptions, and various forms of chronic cutaneous LE [24]. The SLICC criteria introduced an essentially complete list of these manifestations, which, with chronic cutaneous LE, included hypertrophic (verrucous) lupus, lupus panniculitis (lupus profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus and discoid lupus/lichen planus overlap, in addition to localized or generalized classic discoid rash [3]. Most of these other chronic cutaneous LE forms are either uncommon, at least without additional DLE lesions, or less specific, but they do play a role in diagnostic considerations, as do leucocytoclastic or urticarial vasculitis. DLE, in contrast, has been part of all three criteria sets [1–3, 13]. Also introduced with the SLICC criteria [25], scLE has typical lesions and ~40% of the patients with scLE have SLE [26–29], while the other 60% have cutaneous LE only. scLE became a fully independent concept with the EULAR/ACR criteria, carrying a weight of 4, on par with discoid lesions.

acLE is almost entirely associated with SLE. Malar rash, with its butterfly appearance due to nasolabial sparing, is so typical that it has led to butterfly symbols for most lupus foundations and patient associations. However, other skin problems, in particular rosacea, can be misinterpreted as malar rash. Importantly, malar rash is entirely flat without papules or pustules and does not lead to teleangiectasias. Today, photographs may aid verification. Of the other acLE manifestations listed in the SLICC criteria, namely bullous lupus, the toxic epidermal necrolysis variant of SLE, maculopapular lupus rash and photosensitive lupus rash, only the generalized maculopapular rash stayed in the definition of acLE for the EULAR/ACR criteria.

Non-scarring alopecia is another important concept that has been added by the SLICC group [3], and a typical sign, even if of limited specificity. Likewise, oral ulcers are common in SLE but may have many causes. Therefore both alopecia and oral ulcers are part of the EULAR/ACR criteria (Table 1).

All mucocutaneous manifestations need experience to diagnose and treat, and an interdisciplinary approach is often helpful. Biopsies of true lupus lesions have typical features—atypical histology should lead one to discount the lesion for classification [1, 2], but probably also for diagnosis. SLE skin manifestations show ultraviolet (UV) light sensitivity, but reactions to UV light usually tend to take several days [30], while, for example, rosacea reacts almost immediately to sunlight. In line with dermatological suggestions [31], the EULAR/ACR criteria do not include photosensitivity [1, 2], and we also recommend not overrating a history of sun hypersensitivity when considering a diagnosis of SLE. Importantly, both the ACR [13] and SLICC criteria [3] clearly define photosensitivity by a skin rash.

One more lesson of the EULAR/ACR criteria project is that various manifestations in the SLE mucocutaneous domain overlap [4], which may imply that they are different manifestations of the same mucocutaneous autoimmune process. Within the domains, only the highest-weighted item is counted [1, 2]. For routine clinical purposes, this suggests that ANA plus different mucocutaneous lesions are not sufficient for an SLE diagnosis, which would need either specific autoantibodies or additional organ manifestations.

Lupus nephritis

While mucocutaneous SLE manifestations are the most obvious, LN by histology is arguably among the most specific common organ manifestations [32]. Defining renal histology compatible with LN sufficient for SLE classification when combined with ANA or anti-dsDNA antibodies was a major step forward in the SLICC criteria [3]. This has not changed much with the new EULAR/ACR criteria [1, 2]. LN on histology was defined by the International Society of Nephrology/Renal Pathology Society criteria [17, 33]. Subsequently the relative weight for either class II or class V nephritis turned out to be slightly lower, given a greater number of differential diagnoses [34]. With a total of 8 points, class II or V (membranous) nephritis by themselves is not sufficient for classification, while the 10 points of class III or IV nephritis make the cut-off of 10 [1, 2]. Anti-dsDNA antibodies should cause positive ANA, so there is no practical difference from the SLICC criteria.

As an alternative to histology, proteinuria, which is essentially always present in LN, still carries 4 points if above >0.5 g/day in a 24 h urine or an equivalent spot

Table 1 Organ domains in the EULAR/ACR 2019 criteria for and in the diagnosis of SLE

Domain	EULAR/ACR 2019 classification criteria	Other feature relevant for SLE diagnosis
Autoantibodies		
	ANA (obligatory entry criterion)	Anti-Ro/ anti-La
1	Anti-Sm: 6	Anti-U1RNP
	Anti-dsDNA (highly specific test): 6	Anti-dsDNA (tests of lesser specificity)
2	Anti-cardiolipin (medium to high titre): 2	Anti-nucleosome/anti-chromatin
	Anti-β2-glycoprotein I: 2	Anti-histone
	Lupus anticoagulant: 2	Anti-C1q
		Anti-ribosomal P
		Positive Coombs test without haemolysis
		False-positive serology for syphilis
Complement		
3	C3 and C4 low: 4	CH50 low
	C3 or C4 low: 3	Complement split products on erythrocytes
Mucocutaneous manifestations		
4	ACLE: 6	Lupus tumidus
	SCLE: 4	Lupus panniculitis/lupus profundus
	DLE: 4	Chilblains lupus
	Oral ulcers: 2	Leucocytoclastic vasculitis
	Non-scarring alopecia: 2	Urticarial vasculitis
		Nasal ulcers
Lupus nephritis		
5	ISN/RPS class III or IV nephritis: 10	IgA nephritis
	ISN/RPS class II or V nephritis: 8	Cellular casts
	Proteinuria $>$0.5 g/day: 4	
Musculoskeletal manifestations		
6	Joint involvement: 6	Myositis
Serositis		
7	Acute pericarditis: 6	Sterile peritonitis
	Pleural or pericardial effusion: 5	
Neuropsychiatric manifestations		
8	Seizure: 5	(transverse) Myelitis (often APS-related)
	Psychosis: 3	Chorea
	Delirium: 2	Mononeuritis multiplex
		Cranial neuropathy
		Peripheral neuropathy
		Lupus headache
Haematological manifestations		
9	Thrombocytopenia: 4	Thrombotic thrombocytopenic purpura
	Autoimmune haemolytic anaemia: 4	Other forms of haemolytic anaemia
	Leukopenia: 3	Anaemia of chronic disease
		Lymphopenia
Constitutional manifestations		
10	Fever: 2	Arthralgias
		Myalgias
		Fatigue
		Lymphadenopathy
Other uncommon SLE organ manifestations		
		Pneumonitis
		Interstitial lung disease
		Pulmonary arterial hypertension
		Libman–Sacks endocarditis (APS related)
		Myocarditis
		Hepatitis
		Pancreatitis
		Gastrointestinal vasculitis
		Interstitial cystitis

ISN: International Society of Nephrology; RPS: Renal Pathology Society.

urine:creatinine ratio [1, 2]. Cellular casts in the urinary sediment are an important clinical sign of glomerulonephritis [32]. However, urinary sediment was found to be investigator dependent and too easy to change upon glucocorticoid therapy, so was not retained in the EULAR/ACR criteria. For diagnostic purposes, relevant proteinuria should today lead to kidney biopsy [32], if not strictly contraindicated, which will make both the diagnosis and (mostly) the classification easy. The slightly lower points for class V nephritis should serve as a reminder that there are uncommon alternative reasons for membranous nephritis, such as lymphoma, which may also provoke ANA.

Musculoskeletal SLE manifestations

Lupus arthritis is common and, at 6 points, heavily weighted in the EULAR/ACR criteria [1, 2, 34]. Lupus arthritis is typically non-erosive and not associated with anti-CCP antibodies. Erosive and anti-CCP-positive disease is far more likely to be RA, even if an SLE diagnosis is unequivocal. In fact, rhupus denotes the overlap disease between SLE and RA [35]. Depicting this situation has become easy with the general attribution rule of the EULAR/ACR 2019 criteria: an item should only be attributed to SLE (and counted) if there is no more likely alternative explanation [1, 2, 17]. Arthritis should thus not be considered lupus arthritis if RA is more likely, as in anti-CCP-positive arthritis. Lupus arthritis, which damages ligaments and leads to Jaccoud-like changes instead of damaging the bone, often also shows less obvious synovitic swelling than RA, as seen in sonographic studies [36]. In line with these ideas, the SLICC group defined arthritis as either synovitis involving two or more joints characterized by swelling or effusion or tenderness in two or more joints and at least 30 min of morning stiffness [3]. This definition, now termed SLE joint involvement, proved superior to synovitis and was thus retained [1, 2]. These findings should also be considered when diagnosing SLE or evaluating organ involvement in a given patient. Lupus myositis, usually with marked increases in creatinine phosphokinase and muscle enzymes, is another well-defined musculoskeletal SLE manifestation [37], which is too uncommon for classification, but may still be important for the diagnosis. Arthralgias and myalgias, with similar features to the prodromal signs of virus infections and being pathophysiologically related, are common and may guide the diagnosis, they have low specificity for SLE [15].

Lupus serositis

The serosal manifestations of pleuritis and pericarditis are likewise typical signs of SLE that have been present in both ACR and SLICC criteria [3, 13], with some changes in definitions. For pleuritis, pleural effusion is so likely to follow that this more objective finding was adopted for the EULAR/ACR criteria [1, 2]. Acute pericarditis was defined as per the European Society of Cardiology 2015 guidelines [17, 38] and given a slightly higher weight (Table 1). For diagnosis, other causes, including pulmonary embolism and virus pleuritis, are of major importance, which would also lead to not counting this manifestation for SLE in the EULAR/ACR criteria, according to the above-mentioned attribution rule. Much less common, serositis can also take the form of sterile peritonitis [39]. Lupus serositis is one of the few situations where CRP is actually relevantly increased in SLE [40].

Neuropsychiatric SLE

Various autoantibodies and immune complexes in SLE can cause a plethora of NPSLE symptoms [41]. These range from functional disturbances leading to psychosis—such as caused by anti-ribosomal P antibodies, via antibody-mediated cell death, e.g. by autoantibodies to the N-methyl-D-aspartate receptor, and immune complex–mediated CNS vasculitis—to unspecific symptoms like lupus headache. In addition, secondary APS can cause arterial as well as venous sinus thrombosis, and accelerated atherosclerosis is an important differential diagnosis for vascular lesions. Indeed, APS or atherosclerosis cause vascular CNS processes more frequently than vasculitis in SLE [42]. This also demands caution when considering CNS disease in the SLE diagnosis or classification. Therefore the ACR criteria only included psychosis and seizures [13], both of which are typical and fairly specific. The SLICC criteria added mononeuritis multiplex, myelitis and peripheral or cranial neuropathy [3], but all of these additional symptoms are uncommon and rarely important for classifying SLE.

Consequently, the EULAR/ACR 2019 criteria have essentially come back to the NPSLE version of the ACR criteria [13]. In keeping with up-to-date neuropsychiatric definitions, however, delirium, defined by (1) a change in consciousness or level of arousal with reduced ability to focus, (2) symptom development over hours to <2 days, (3) symptom fluctuation throughout the day and either (4a) acute/subacute change in cognition or (4b) change in behaviour, mood or affect, is now differentiated from psychosis, defined as delusions and/or hallucinations without insight and no delirium [17]. This is in fact similar to the SLICC criteria, where psychosis and acute confusional state were listed separately [3].

For diagnostic purposes, however, it is important to realize that the less common and less specific neuropsychiatric manifestations, including those listed in the SLICC criteria [3], but also chorea [42] and lupus headache [41, 43], may play a role for the diagnosis. Importantly, other disease, infections in particular, need to be ruled out in the diagnostic process [42]. The EULAR/ACR criteria attribution rule that manifestations are more likely caused by another problem than SLE itself, e.g. APS, needs to be followed and should also be honoured in diagnosis.

Haematological SLE manifestations

In contrast to the inflammatory organ manifestations induced by immune complexes, the typical lupus cytopenias in the various lines of blood cells are directly caused by autoantibodies, most of which cannot be routinely measured. This also makes attribution more challenging. The obvious exception is autoimmune haemolytic anaemia, established by a positive Coombs test in addition to objective signs of haemolysis, including decreased haptoglobin, increased reticulocytes and elevated lactate dehydrogenase levels [1, 2]. Other forms of haemolysis, such as microangiopathic haemolysis with schistocytes, are also possible in SLE, but much less specific. Therefore the EULAR/ACR criteria demand a positive Coombs test [1, 2]. Much more common, but completely unspecific, is anaemia of chronic disease, which in the diagnostic approach still argues for ongoing inflammation, whatever the cause [44].

Thrombocytopenia in SLE can be similar to idiopathic thrombocytopenic purpura, and indeed a proportion of idiopathic thrombocytopenic purpura patients will manifest SLE later on. Lupus thrombocytopenia is typically not associated with measurable autoantibodies. It is therefore important to rule out other causes, and aPL antibodies in particular, before attributing thrombocytopenia to SLE. The same exclusion approach also applies to diagnosing SLE.

Leukopenia is a common manifestation of SLE, but can also have numerous other causes, including drugs like azathioprine or metamizole, infection, haematological disease and Felty syndrome [25], which need to be ruled out. While the ACR criteria demanded two independent measurements of leucocytes $<4000/mm^3$ [13], the SLICC group showed that a single measurement is actually superior [3], which was confirmed within the EULAR/ACR classification criteria project [1, 2]. Lymphopenia, defined as $<1500/mm^3$ twice in the ACR criteria [13] and as $<1000/mm^3$ once in the SLICC criteria [3], is an extremely common but unspecific finding, which was therefore not voted into the final set of criteria by the external experts in the nominal group exercise for the EULAR/ACR criteria [18]. For diagnostic purposes, lymphopenia needs to be taken into account but should not be overinterpreted.

Constitutional symptoms in SLE

Non-infectious fever is the one criterion that is entirely new in the EULAR/ACR 2019 classification criteria, carrying a weight of 2, but helping with early classification [1, 2]. Fever came not from the expert Delphi exercise [11], but was a common and specific marker of SLE in the international early SLE cohort [15], where 35% of the SLE patients *vs* 14% of those with mimicking conditions had fever and 28% *vs* 8% had fever without increased CRP. Similarly, in the SLE patient questionnaire, 54% of the patients reported fever before or at their SLE diagnosis [43]. For fever, adhering to the attribution rule of not counting a criterion better explained by another cause is of obvious importance. Fever with elevated CRP is particularly likely to be due to bacterial infection [44].

As an immune complex disease, other features of SLE likewise are similar to viral infections. Classic features of early viral disease, namely arthralgias, myalgias and fatigue, are often pronounced and of persistence in SLE [43, 45]. However, arthralgias (in the absence of arthritis) and fatigue were actually more common in mimicking conditions than in SLE patients [15], and the same probably would be true for myalgias as well. This is important information when considering these symptoms for SLE diagnosis. One other relatively common constitutional symptom is lymphadenopathy, which often necessitates lymph node biopsy to rule out lymphoma.

Other uncommon manifestations

Since SLE can afflict practically every single organ, there is a wide variety of manifestations so uncommon and/or usually associated with multiple other manifestations that they were not included in any of the classification criteria sets. For example, it is important to remember that SLE lung disease may include lupus pneumonitis, interstitial lung disease and pulmonary arterial hypertension [46]; that myocardiac involvement is possible [47] and that APS in SLE may cause Libman–Sacks endocarditis [48]. Likewise, lupus hepatitis, lupus pancreatitis and of course gastrointestinal vasculitis [39] are possible manifestations, as is interstitial cystitis [49]. All of these would certainly support an SLE diagnosis once other causes have been ruled out.

Conclusions

The EULAR/ACR 2019 criteria maintained specificity at the level of the ACR criteria and increased sensitivity almost to the level of the SLICC criteria, but erring on the side of higher specificity, where necessary. This and the attempt to keep the list relatively short have led to the exclusion of uncommon criteria items and of lymphopenia. Some of this reductionist approach has been criticized. We think that it was necessary for classification, and the EULAR/ACR criteria were designed for classification, not diagnosis. Even though the same formally holds true for the SLICC criteria, their considerably longer list contains additional items that may play a role in diagnosing SLE. Likewise, many of the exclusions listed in the ACR and SLICC criteria may be good reminders.

Twenty years into the 21st century, both SLE classification and diagnosis still rely on clinical manifestations and autoimmune serology. While modern science approaches will change this approach at some point, we do not expect major changes in the near future. However, additional markers, e.g. the type I interferon signature [50, 51], may well add to our repertoire of meaningful tests relatively soon, presumably starting with diagnosis and finding their way into classification once established worldwide. For

classification, the EULAR/ACR 2019 criteria [1, 2] are now the standard, and many of their central rules, some taken from the older ACR [13, 14] and SLICC criteria [3], also educate diagnostic thinking: it is important to have both clinical and immunological findings, and most SLE patients are ANA positive. SLE manifestations may develop over time and need not exist simultaneously. Items should only be attributed to SLE if there are no explanations that are more likely [17]. Manifestations within one organ domain are interrelated and not independent of each other [4]. Items do have different weights in reality, which for the list of criteria have been quantified in the EULAR/ACR criteria approach [1, 2]. What all these facts show is a disease manifested by several autoantibodies and immune complexes and the resulting variable organ manifestations [5, 7, 8].

Funding: While the SLE classification criteria project was jointly supported by the EULAR and ACR, there was no financial support for this article. No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article. This paper was published as part of a supplement supported by an educational grant from GSK.

Disclosure statement: MA and SRJ served as co-chairs of the EULAR/ACR classification criteria steering committee.

References

1 Aringer M, Costenbader K, Daikh D *et al.* 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:1151–9.

2 Aringer M, Costenbader K, Daikh D *et al.* 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol 2019;71:1400–12.

3 Petri M, Orbai AM, Alarcon GS *et al.* Derivation and validation of systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

4 Touma Z, Cervera R, Brinks R *et al.* Associations among classification criteria items within systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2019;doi: 10.1002/acr.24078.

5 Aringer M, Dorner T, Leuchten N, Johnson SR. Toward new criteria for systemic lupus erythematosus-a standpoint. Lupus 2016;25:805–11.

6 Johnson SR, Goek ON, Singh-Grewal D *et al.* Classification criteria in rheumatic diseases: a review of methodologic properties. Arthritis Rheum 2007;57:1119–33.

7 Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011;365:2110–21.

8 Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008;358:929–39.

9 Wallace DJ, Stohl W, Furie RA *et al.* A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum 2009;61: 1168–78.

10 Leuchten N, Hoyer A, Brinks R *et al.* Performance of anti-nuclear antibodies for classifying systemic lupus erythematosus: a systematic literature review and meta-regression of diagnostic data. Arthritis Care Res (Hoboken) 2018;70:428–38.

11 Schmajuk G, Hoyer BF, Aringer M *et al.* Multicenter Delphi exercise to identify important key items for classifying systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2018;70:1488–94.

12 Pisetsky DS, Spencer DM, Lipsky PE, Rovin BH. Assay variation in the detection of antinuclear antibodies in the sera of patients with established SLE. Ann Rheum Dis 2018;77:911–3.

13 Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.

14 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40: 1725.

15 Mosca M, Costenbader KH, Johnson SR *et al.* Brief report: how do patients with newly diagnosed systemic lupus erythematosus present? A multicenter cohort of early systemic lupus erythematosus to inform the development of new classification criteria. Arthritis Rheumatol 2019;71:91–8.

16 Choi MY, FitzPatrick RD, Buhler K, Mahler M, Fritzler MJ. A review and meta-analysis of anti-ribosomal P autoantibodies in systemic lupus erythematosus. Autoimmun Rev 2020;19:102463.

17 Tedeschi SK, Johnson SR, Boumpas D *et al.* Developing and refining new candidate criteria for systemic lupus erythematosus classification: an international collaboration. Arthritis Care Res (Hoboken) 2018;70:571–81.

18 Johnson SR, Khanna D, Daikh D *et al.* Use of consensus methodology to determine candidate items for systemic lupus erythematosus classification criteria. J Rheumatol 2019;46:721–6.

19 Harris EN, Gharavi AE, Boey ML *et al.* Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet 1983;322:1211–4.

20 Khamashta MA, Bertolaccini ML, Hughes GR. Antiphospholipid (Hughes) syndrome. Autoimmunity 2004;37:309–12.

21 Miyakis S, Lockshin MD, Atsumi T *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.

22 Mosca M, Tani C, Aringer M *et al.* European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis 2010;69:1269–74.

23 Carroll MC. The lupus paradox. Nat Genet 1998;19:3–4.

24 Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. Best Pract Res Clin Rheumatol 2013;27:391–404.

25 Petri M, Orbai AM, Alarcon GS *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

26 Tiao J, Feng R, Carr K, Okawa J, Werth VP. Using the American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) criteria to determine the diagnosis of systemic lupus erythematosus (SLE) in patients with subacute cutaneous lupus erythematosus (SCLE). J Am Acad Dermatol 2016;74:862–9.

27 Chlebus E, Wolska H, Blaszczyk M, Jablonska S. Subacute cutaneous lupus erythematosus versus systemic lupus erythematosus: diagnostic criteria and therapeutic implications. J Am Acad Dermatol 1998;38: 405–12.

28 Vera-Recabarren MA, García-Carrasco M, Ramos-Casals M, Herrero C. Comparative analysis of subacute cutaneous lupus erythematosus and chronic cutaneous lupus erythematosus: clinical and immunological study of 270 patients. Br J Dermatol 2010;162:91–101.

29 Grönhagen CM, Fored CM, Granath F, Nyberg F. Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden. Br J Dermatol 2011; 164:1335–41.

30 Kuhn A, Sonntag M, Richter-Hintz D *et al.* Phototesting in lupus erythematosus: a 15-year experience. J Am Acad Dermatol 2001;45:86–95.

31 Albrecht J, Berlin JA, Braverman IM *et al.* Dermatology position paper on the revision of the 1982 ACR criteria for systemic lupus erythematosus. Lupus 2004;13: 839–49.

32 Bertsias GK, Tektonidou M, Amoura Z *et al.* Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771–82.

33 Weening JJ, D'Agati VD, Schwartz MM *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521–30.

34 Tedeschi SK, Johnson SR, Boumpas DT *et al.* Multicriteria decision analysis process to develop new classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:634–40.

35 Tani C, D'Aniello D, Sedie AD *et al.* Rhupus syndrome: assessment of its prevalence and its clinical and instrumental characteristics in a prospective cohort of 103 SLE patients. Autoimmun Rev 2013;12:537–41.

36 Zayat AS, Mahmoud K, Md Yusof MY *et al.* Defining inflammatory musculoskeletal manifestations in systemic lupus erythematosus. Rheumatology (Oxford) 2019;58: 304–12.

37 Record JL, Beukelman T, Cron RQ. High prevalence of myositis in a southeastern United States pediatric systemic lupus erythematosus cohort. Pediatr Rheumatol Online J 2011;9:20.

38 Adler Y, Charron P, Imazio M et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2015;36:2921–64.

39 Fawzy M, Edrees A, Okasha H, El Ashmaui A, Ragab G. Gastrointestinal manifestations in systemic lupus erythematosus. Lupus 2016;25:1456–62.

40 Ueki K, Ikeuchi H, Ota F *et al.* Extremely high levels of C-reactive protein in patients with acute lupus serositis. Mod Rheumatol 2002;12:267–70.

41 ACR ad hoc committee on neuropsychiatric lupus nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.

42 Bertsias GK, Ioannidis JP, Aringer M *et al.* EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69: 2074–82.

43 Leuchten N, Milke B, Winkler-Rohlfing B *et al.* Early symptoms of systemic lupus erythematosus (SLE) recalled by 339 SLE patients. Lupus 2018;27:1431–6.

44 Aringer M. Inflammatory markers in systemic lupus erythematosus. J Autoimmun 2020;110:102374.

45 Bauernfeind B, Aringer M, Prodinger B *et al.* Identification of relevant concepts of functioning in daily life in people with systemic lupus erythematosus: a patient Delphi exercise. Arthritis Rheum 2008;61:21–8.

46 Hannah JR, D'Cruz DP. Pulmonary complications of systemic lupus erythematosus. Semin Respir Crit Care Med 2019;40:227–34.

47 Tanwani J, Tselios K, Gladman DD, Su J, Urowitz MB. Lupus myocarditis: a single center experience and a comparative analysis of observational cohort studies. Lupus 2018;27:1296–302.

48 Tincani A, Rebaioli CB, Taglietti M, Shoenfeld Y. Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. Rheumatology (Oxford) 2006;45(Suppl 4):iv8–13.

49 Koh JH, Lee J, Jung SM *et al.* Lupus cystitis in Korean patients with systemic lupus erythematosus: risk factors and clinical outcomes. Lupus 2015;24:1300–7.

50 Brohawn PZ, Streicher K, Higgs BW *et al.* Type I interferon gene signature test-low and -high patients with systemic lupus erythematosus have distinct gene expression signatures. Lupus 2019;28:1524–33.

51 Catalina MD, Owen KA, Labonte AC, Grammer AC, Lipsky PE. The pathogenesis of systemic lupus erythematosus: harnessing big data to understand the molecular basis of lupus. J Autoimmun 2020;110: 102359.