The New EULAR/ACR Criteria for Classification of SLE in Action

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On behalf of the EULAR/ACR
SLE Criteria Development Subcommittee

Disclosures

• EULAR/ACR support for the development of SLE classification criteria
• No other financial or other relationships to disclose

Pondering whether you have SLE patients eligible for the new quasilimumab trial...

Your first patient

• A 44 year old woman with a 10 year history of mild SLE. She originally came to see you for fatigue and arthralgias.
• She had a +ANA 1:160 speckled on Hep2 immunofluorescence (IF) several years ago. She has recurrent oral ulcers, Raynaud’s phenomenon, headaches, and one episode of idiopathic pericarditis with a small pericardial effusion on ECHO several years ago.
• She is now taking hydroxychloroquine.
• Her labs show lowest WBC count 3,200/mm³, normal hemoglobin, normal platelet count, normal kidney function.
• Anti-Ro, anti-La, anti-dsDNA are positive and C4 has been low in the past. Anti-Smith is negative.
Your first patient

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• She is now taking hydroxychloroquine.
• Her labs show lowest WBC count 3,200/mm³, normal hemoglobin, normal platelet count, normal kidney function.
• Anti-Ro, anti-La, anti-dsDNA are positive and C4 has been low in the past. Anti-Smith is negative.

Inclusion Criterion

• + ANA 1:80 or greater on HEp2 IF

“Opening Statements”

• For each criterion, do not score if a cause more likely than SLE exists (such as infection, malignancy, medication, rosacea, endocrine disorder, other autoimmune disease).
• Occurrence of a criterion on at least one occasion is sufficient.
• Individual criteria need not occur simultaneously.
• At least one clinical criterion must be present.
• Within each domain, only the highest weighted criterion is counted toward the total score.

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• She is now taking hydroxychloroquine.
• Her labs show lowest WBC count 3,200/mm³, normal hemoglobin, normal platelet count, normal kidney function.
• Anti-Ro, anti-La, anti-dsDNA are positive and C4 has been low in the past. Anti-Smith is negative.
Muco-cutaneous Domain Definitions

- Oral ulcers
- Oral ulcers*
- Subacute cutaneous lupus (SCLE) or discoid lupus (DLE):
  - SCLE: annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed.* **
  - DLE: erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp.* **
- Acute cutaneous lupus: Malar rash (localized) or maculopapular rash (generalized) with or without photosensitivity.* **

*Observed by clinician. Direct observation may include physical examination or review of a photograph.
**If skin biopsy is performed, typical changes must be present.

Merola J et al, proposed Cutaneous Lupus Definitions

Your first patient

- A 44 year old woman with a 10 year history of mild SLE. She originally came to see you for fatigue and arthralgias.
- She has a +ANA 1:160 speckled on HEp2 IF several years ago. She has recurrent oral ulcers, Raynaud's phenomenon, headaches, and one episode of idiopathic pericarditis with a small pericardial effusion on ECHO several years ago.
- She is now taking hydroxychloroquine.
- Her labs show lowest WBC count 3,200/mm³, normal hemoglobin, normal platelet count, normal kidney function.
- Anti-Ro, anti-La, anti-dsDNA are positive and C4 has been low in the past. Anti-Smith is negative.

Serositis Domain Definitions

- Pleural or pericardial effusion: imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both, not meeting the definition of acute pericarditis below
- Acute pericarditis: ≥2 of (1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), (2) pericardial rub, (3) EKG with new widespread ST-elevation or PR depression, (4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)

Hematologic Domain Definitions

- Leukopenia: WBC <4,000/mm³
- Thrombocytopenia: Platelets <100,000/mm³
- Autoimmune hemolysis with: (1) evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH and (2) positive Coomb's (direct antiglobulin test)
Your first patient

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• She has a +ANA 1:160 speckled on HEp2 IF several years ago. She has recurrent oral ulcers, Raynaud’s phenomenon, headaches, and one episode of idiopathic pericarditis with a small pericardial effusion on ECHO several years ago.
• She is now taking hydroxychloroquine.
• Her labs show lowest WBC count 3,200/mm³, normal hemoglobin, normal platelet count, normal kidney function.
• Anti-Ro, anti-La, anti-dsDNA are positive and C4 has been low in the past. Anti-Smith is negative.

Immunologic Domains Definitions

Antiphospholipid antibodies
Anticardiolipin antibody positive (medium or high units) or anti-β2 GP1 positive or lupus anticoagulant positive

Complement proteins
Low C3 or low C4
Low C3 and low C4

Highly specific antibodies
Anti-dsDNA
Anti-Smith antibody
Your second patient

- A 32 year old man is newly seen for a + ANA of 1:320 on HEp2 IF. He has had no fevers, oral ulcers, alopecia, or malar rash.
- On physical exam, there were no lesions of subacute cutaneous lupus or discoid lupus. A diffuse maculopapular rash was observed, but was not biopsied. The musculoskeletal exam revealed no synovitis. The neurologic exam was normal. He reported no chest pain and there was no evidence of pleural or pericardial effusion.
- Complete blood counts were notable for lowest white blood cell count 4200/mm$^3$, platelet count 11,000/mm$^3$, and no evidence of hemolysis.
- Urinalysis revealed no red blood cells or proteinuria. Anti-phospholipid antibodies, C3, C4, anti-dsDNA, and anti-Smith were all normal/negative.

Inclusion Criterion

- + ANA 1:80 or greater on HEp2 IF

Muco-cutaneous Domain Definitions

- Non-scarring alopecia*
- Oral ulcers*
- Subacute cutaneous lupus (SCLE) or discoid lupus (DLE):
  - SCLE: annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed.* **
  - DLE: erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp.* **
- Acute cutaneous lupus: Malar rash (localized) or maculopapular rash (generalized) with or without photosensitivity.* **

Hematologic Domain Definitions

- Leukopenia: WBC <4,000/mm$^3$
- Thrombocytopenia: Platelets <100,000/mm$^3$
- Autoimmune hemolysis: (1) evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH and (2) positive Coomb’s (direct antiglobulin test)

*Observed by clinician. Direct observation may include physical examination or review of a photograph.
**If skin biopsy is performed, typical changes must be present.
Merola J et al, proposed Cutaneous Lupus Definitions
Your third patient

A 24 year old woman with a + ANA of 1:80 on HEp2 IF.
She had no history of fevers, oral ulcers, alopecia, or other rashes. She had not had any arthritis. She had not had any symptoms of delirium, psychosis, or seizures, or other neurologic abnormalities. She had had no symptoms of pleuritis or pericarditis. Her blood counts had been normal. She had had heavy proteinuria and a renal biopsy showed membranous glomerulonephritis with immunofluorescent deposits, consistent with class V lupus nephritis.
She did not have any antiphospholipid antibodies. Her complement levels were normal. Anti-dsDNA and anti-Smith antibodies were negative.

Renal Domain Definitions

- **Proteinuria >0.5g/24h**: on 24 hour urine collection or spot urine protein-to-creatinine ratio representing >0.5g protein/24h
- **Renal Biopsy with Class II or V lupus nephritis**
- **Renal Biopsy with Class III or IV lupus nephritis**

*International Society of Nephrology/Renal Pathology Society definitions*

**Class II**: Mesangial proliferative lupus nephritis: Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.

**Class III**: Focal lupus nephritis: Active or inactive focal, segmental or global endo-or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.

**Class IV**: Diffuse lupus nephritis: Active or inactive diffuse, segmental or global endo-or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.

**Class V**: Membranous lupus nephritis: Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations.

**Class VI**: Advanced sclerotic lupus nephritis: ≥90% of glomeruli globally sclerosed without residual activity.

Clinical Domains

1. Constitutional: Unexplained fever >38.3 C
2. Mucocutaneous: Non-scarring alopecia
   Oral ulcers
   Subacute cutaneous lupus or discoid lupus
   Acute cutaneous lupus
3. Arthritis: Synovitis in 2 or more joints
4. Neurologic:
   Delirium
   Psychosis
   Seizure
5. Serositis:
   Pleural or pericardial effusion
   Acute pericarditis
6. Hematologic:
   Leukopenia
   Thrombocytopenia
   Autoimmune hemolysis
7. Renal:
   Proteinuria
   Renal biopsy - Class II or V lupus nephritis
   Renal biopsy - Class III or IV lupus nephritis

Immunologic Domains

8. Antiphospholipid Antibodies:
   Present
9. Complement levels:
   Low C3 or C4
   Low C3 and C4
10. Specific antibodies
    Anti-dsDNA
    Anti-Smith

SUBMIT

Your last patient

A 56 year old man patient had a + ANA of 1:2560 on Hep2 IF. He did not have fevers, oral ulcers, alopecia, or any rashes. He had arthritis of the small joints of the hands and feet, with physician-observed synovitis in the right MCP2 and 4, in the left MCP3 and 4 and PIP4, in the right wrist, and the right forefoot. Plain radiographs were obtained and showed erosions. An anti-CCP antibody was obtained and was in the high positive range (greater than 3 times the upper limit of normal). The patient had had no delirium, psychosis or delusions, or motor or sensory nerve disturbances. He has a history of grand mal seizures. He had not had any pleuritis or pericarditis. His anti-cardiolipin IgG was elevated at 81 units. Anti-β2 GP1 and lupus anticoagulant antibodies were negative. His complements were in the normal ranges. His anti-dsDNA and anti-Smith antibodies were negative.
Arthritis Domain Definition

- **Synovitis in ≥2 joints**: characterized by joint swelling and tenderness, directly observed.
- “Opening statement”: For each criterion, do not score if a cause more likely than SLE exists.
- You think he has seropositive, erosive RA causing his small joint polyarthritis.

Your last patient

A 56 year old man patient had a + ANA of 1:2560 on HEp2 IF. He did not have fevers, oral ulcers, alopecia, or any rashes. He had had arthritis of the small joints of the hands and feet, with physician-observed synovitis in the right MCP2 and 4, in the left MCP3 and 4 andPIP4, in the right wrist, and the right forefoot. Plain radiographs were obtained and showed erosions. An anti-CCP antibody was obtained and was in the high positive range (greater than 3 times the upper limit of normal). The patient had had no delirium, psychosis or delusions, or motor or sensory nerve disturbances. He had a history of grand mal seizures. He had not had any pleuritis or pericarditis.

His anti-cardiolipin IgG was elevated at 81 units. Anti-β2 GP1 and lupus anticoagulant antibodies were negative. His complements were in the normal ranges. His anti-ds DNA and anti-Smith antibodies were negative.

Neurologic Domain Definitions

- **Delirium**: (1) 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 behavior, mood or affect
- **Psychosis**: (1) delusions and/or hallucinations without insight and (2) absence of delirium
- **Seizure**: primary generalized seizures or partial/focal seizures with independent description by a reliable witness

Your last patient

A 56 year old man patient had a positive ANA of 1:2560 on HEp2 immunofluorescence. He did not have fevers, oral ulcers, alopecia, or any rashes. He had had arthritis of the small joints of the hands and feet, with physician-observed synovitis in the right MCP II and IV, in the left MCPIII and IV and PIP IV, in the right wrist, and the right forefoot. Plain radiographs were obtained and showed erosions. An anti-CCP antibody was obtained and was in the high positive range (greater than 3 times the upper limit of normal). The patient had had delirium, no history of psychosis or delusions, or motor or sensory nerve disturbances. He has a history of grand mal seizures. He had not had any pleuritis or pericarditis.

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Immunologic Domains Definitions

**Antiphospholipid antibodies**
- **Anticardiolipin antibody positive (medium or high units)** or anti-β2-GP1 positive or lupus anticoagulant positive

**Complement proteins**
- Low C3 or low C4
- Low C3 and low C4

**Highly specific antibodies**
- Anti-dsDNA
- Anti-Smith antibody
**Immunologic Domains**

8. Antiphospholipid Antibodies:
   - Present
9. Complement levels:
   - Low C3 or C4
   - Low C3 and C4
10. Specific antibodies
    - Anti-dsDNA
    - Anti-Smith

**Strengths**

- Combination of expert-based and data-driven multi-step rigorous criteria development process
- Started from scratch with new item generation, and iterative process to reduce, define and determine independence and weights of criteria
- > 150 SLE experts and centers from around the world participated
- Real cases
- Weighted criteria with ability to classify patients with single organ system involvement
- Excellent performance characteristics (to date)
- Ongoing large and rigorous validation

**Limitations and Points for Discussion**

- SLE is heterogeneous: large spectrum of disease including overlap syndromes, incomplete lupus, pre-SLE, possible SLE, cutaneous-only lupus
- Overlap syndromes can be classified as SLE if meet SLE criteria. Could be excluded in specific studies.
- Newer biomarkers and assays, such as complement deposition products and interferon signatures, may be very helpful in distinguishing SLE from non-SLE, but not widely used and available at this time.
- Somewhat complicated system (but that’s what computers and smart phones are for!)

**Acknowledgments**

Combination of expert-driven multi-step criteria development process initiated by a group of over 150 SLE experts and centers from around the world. Real cases were included to ensure the criteria had ability to classify patients with single organ system involvement. Excellent performance characteristics (to date) were achieved through ongoing large and rigorous validation.

**Debate Points**

- SLE is heterogeneous: large spectrum of disease including overlap syndromes, incomplete lupus, pre-SLE, possible SLE, cutaneous-only lupus. Overlap syndromes can be classified as SLE if meet SLE criteria. Could be excluded in specific studies.
- Newer biomarkers and assays, such as complement deposition products and interferon signatures, may be very helpful in distinguishing SLE from non-SLE, but not widely used and available at this time.
- Somewhat complicated system (but that’s what computers and smart phones are for!)

**Your patient has 7 points, not enough to be classified as SLE.**
Muco-cutaneous Domain Definitions

*Typical skin biopsy histopathology* (based upon an international Delphi consensus process at the 2013 International Meeting on Cutaneous Lupus Erythematosus):

- **SCLE**: interface vacuolar dermatitis consisting of a peri-vascular lymphohistiocytic infiltrate, often with dermal mucin noted
- **DLE**: interface vacuolar dermatitis consisting of a peri-vascular and/or peri-appendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition and basement membrane thickening may be noted.
- **Acute cutaneous lupus**: interface vacuolar dermatitis consisting of a peri-vascular lymphohistiocytic infiltrate, often with dermal mucin noted. Peri-vascular neutrophilic infiltrate may be present early in the course.

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