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Systemic lupus erythematosus: pearls and paradigms

Systemic *lupus erythematosus* (SLE) is a systemic autoimmune disease characterized by autoantibody and immune complex formation which results in multi-organ inflammation. The purpose of this discussion is to improve the clinical understanding of SLE and to increase the clinician's comfort level in making a diagnosis of lupus. Furthermore, we will describe a general treatment paradigm for SLE.

SLE is a heterogeneous disorder with a wide variety of presentations. The typical organ systems involved are the central nervous system (CNS), cardiovascular system, pulmonary, skin, mucous membranes, renal, joints, hematopoietic, lymphatics, gastrointestinal and muscle. The American College of Rheumatology (ACR) Classification Criteria state that 4 of the 11 criteria listed in Table 1 must be present over time, or simultaneously, for a patient to be classified as having SLE. In 1997, the classification criteria were modified to include antibody to native DNA (anti-DNA ab), Smith nuclear antigen (anti-Sm ab) and antiphospholipid antibody (aPL). aPL is further defined as abnormal levels of IgG or IgM anticardiolipin (acL), a positive test for lupus anticoagulant (LA), or a false positive test for syphilis present for greater than 6 months duration (1).

Table 1. Classification of SLE – 1997 revised ACR criteria

1	Malar Rash: fixed erythema, flat or raised over the malar eminences, tending to spare the nasolabial folds
2	Discoid Rash: erythematous raised patches with adherent keratotic scaling and follicular plugging
3	Photosensitivity: skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4	Oral ulcers: oral or nasopharyngeal ulceration, usually painless, observed by a physician
5	Arthritis: non-erosive arthritis involving two or more peripheral joints
6	Serositis: pleuritis or pericarditis
7	Renal disorder: persistent proteinuria greater than 0.5 g per day, pr greater than 3+ or cellular casts
8	Neurological disorder: seizures or psychosis in the absence of offending drugs or known metabolic disorders.
9	Hematological disorder: hemolytic anemia with reticulocytosis or leucopenia or thrombocytopenia or lymphopenia
10	Immunological disorder: antiphospholipid, anti-dsDNA or anti-Smith antibody.
11	Antinuclear antibody

It is important to understand the difference between classification and diagnostic criteria and how they apply to making a diagnosis of SLE in an individual patient. Classification criteria for a given disease select those clinical findings which both identify the disease and separate it from other patients who are ill. As a result, classification criteria do not include the full spectrum of

manifestations of a disease (2). With regard to SLE, the ACR classification criteria help us to distinguish patients with SLE from patients with other systemic connective tissue diseases, for example, scleroderma. Conversely, diagnostic criteria tend to focus on a combination of findings that must be present in order to be certain that a patient has a particular disease. Manifestations that are not unique to the disease, but that are found in related conditions are likely to be included in diagnostic criteria (2). With regard to SLE, diagnostic criteria differentiate those with disease from those without disease. For example, the presence of hypocomplementemia is characteristic of SLE and is an indicator of disease activity that is often useful in making the diagnosis of SLE. However, hypocomplementemia is not specific for SLE and may be found in other disorders such as Sjögren's syndrome. To summarize, classification criteria are useful to define a homogeneous study population, while diagnostic criteria are useful for making a clinical diagnosis. In our everyday clinical practices, we often use classification criteria as a reference, not as an absolute set of criteria that must be met for a patient to be diagnosed with lupus. For example, if a 16-year-old female presents with a high titer ANA and psychosis without other clinical findings, she may still be diagnosed with SLE even though she does not meet 4 of the 11 ACR classification criteria for SLE.

CASES REPORT

We will now review some specific cases and the application of specific laboratory testing that we currently have available.

Case 1. A 26-year-old African American female is referred to you with the following clinical manifestations: hematocrit 32% (normal 36–47%), fatigue, arthralgias, history of facial rash, migraine headaches and positive ANA (1:160). On physical examination, she has no rash or mucous membrane ulceration and her joint and neuromuscular exam is normal. First, does this patient have SLE and which features of her presentation are consistent with SLE? Also, which laboratory tests would significantly impact your post-test probability of this patient having SLE? Let's start with a discussion of this patient's anemia and ask what type of anemia is specific for SLE? Furthermore, which lab tests would you order to investigate her anemia? The ACR classification criteria define a hematologic disorder in SLE as any of the following: hemolytic anemia with reticulocytosis, leukopenia (less than 4000 K/mm^3 on two or more occasions), lymphopenia (less than 1500 K/mm^3 on two or more occasions) or thrombocytopenia (less than 100 K/mm^3 in the absence of offending drugs) (1). Further laboratory evaluation of our patient revealed a mean corpuscular volume (MCV) of 72 fL (normal 80–100 fL) and reticulocyte count of 1.2%. A direct Coomb's test (DAT) was negative and the haptoglobin and iron studies were normal. This patient's anemia did not therefore meet the ACR classification criteria for a hematological abnormality present in lupus. Next, let us comment about this patient's fatigue. Fatigue is a non-specific manifestation of SLE. Other non-specific manifestations include malaise, fever and unintentional weight loss. All of these symptoms may be seen in any number of diseases and autoimmune syndromes, therefore they are not considered specific to SLE. This patient also presented with arthralgias, a common but also nonspecific symptom in SLE. The ACR classification criteria define joint involvement in SLE as a non-erosive arthritis, involving two or more peripheral joints characterized by joint tenderness, swelling or effusion (1). Our patient also presented with migraine headaches. Migraine headaches are a common manifestation in lupus but are a nonspecific disease manifestation. The ACR classification criteria define SLE neurological involvement as seizures or psychosis, in the absence of offending drugs or known metabolic derangements. Let us now discuss the positive ANA titer. ANA is the hallmark laboratory of SLE and has a sensitivity of 99% by indirect immunofluorescence assay (IFA). Additionally, in healthy subjects with a positive ANA, the titer tends to be lower (less than or equal to 1:160)

in contrast to the diseased population where the titer is often greater than 1:160. Let us consider then if the positive ANA was normal or abnormal in our patient? More than 99% of patients with SLE have a positive ANA. Conversely, only 5% of the population with a positive ANA has SLE. To put this in perspective, approximately 10 million residents in the United States have a positive ANA without having SLE. Further laboratory testing in our patient revealed the following normal or negative results: blood urea nitrogen (BUN) and creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), dsDNA, extractable nuclear antigens (ENA), lupus anticoagulant (LA) and anticardiolipin antibodies (ačL). The complement levels (C3/C4) and urinalysis were normal. The anemia evaluation was consistent with thalassemia and radiographs of the hands and chest were normal.

Case 1 assessment. The patient is a 26-year-old African American female with nonspecific symptoms of fatigue and arthralgias in association with migraine headaches and mild immunologic dysfunction, as manifested by a low titer positive ANA. Currently she has no other evidence of immune dysfunction or activation. Her management is symptom directed and does not require immune modifying drugs.

Case 2. The patient is a 42-year-old Caucasian female who presented 10 years ago with discoid lupus and a positive ANA (1:320). One year later, she experienced pain and swelling in her hands and was treated with prednisone, hydroxychloroquine (HCQ), and a non-steroidal anti-inflammatory drug (NSAID). One year later she again experienced a flare of arthritis and at this time her ANA was positive at 1:1280. Additional serologic tests showed positive Smith (Sm) and U1-RNP antibodies and a negative rheumatoid factor (RF). Two years later, she experienced increasing fatigue, myalgias and pain in her knees and was diagnosed with patellofemoral syndrome. At this time, an aCL IgG was positive at 153 GPL (normal 0–12 GPL). Does this patient have SLE? What features of her presentation are consistent with a diagnosis of SLE and what features are nonspecific? First, we will discuss discoid *lupus erythematosus* (DLE). DLE is one of the four classic skin manifestations of SLE (1). It is described as a localized or generalized scarring rash that usually appears on the face, ears or scalp. The biopsy of discoid lesions reveals hyperkeratosis of the epidermis, follicular plugging, edema and a mononuclear cell infiltrate at the dermal-epidermal junction (3). Approximately 5–10% of patients that present with classic DLE will eventually develop SLE. This is particularly true for DLE patients with a positive ANA and with lesions below the head and neck. Conversely, 25% of patients with SLE will develop DLE. The patient also had a history of pain and swelling in her hands. As discussed in the previous case, the arthritis of SLE is typically non-erosive, peripheral and symmetric and usually involves the small joints of the hands and wrists. Patients that have arthritis may also be RF positive and approximately 10% of those with arthritis will have nodules. If the arthritis of lupus does result in deformities due to ligamentous laxity, it is called Jacoud's arthropathy. Next, let us comment on the patient's autoantibody profile. The patient had positive Sm and U1-RNP antibodies. Anti-Sm is very specific for SLE (95%), but not very sensitive (30%). Anti-U1-RNP is not very specific and is seen in a wide variety of connective tissue diseases such as mixed connective tissue disease and myositis. Anti-dsDNA, like anti-Sm, has a very high specificity for SLE (95–99%) and a low sensitivity (40%); most commonly it is present in patients that have *lupus nephritis*. Other antibodies that may be present in SLE are antiSS-A (Ro), anti-SS-B (La) and antiphospholipid antibodies (aPL). Anti SS-A antibodies are associated with subacute cutaneous lupus (SCLE) and also with neonatal lupus. aPLs are a family of antibodies that are seen in 50% of patients with SLE and they are associated with the antiphospholipid antibody syndrome (APS), manifested by recurrent miscarriage, venous and arterial thromboses and thrombocytopenia.

Case 2 assessment. The patient is a 42-year-old Caucasian female with multiple clinical manifestations of SLE to include skin involvement, arthritis and autoantibody formation, resulting

in autoimmune dysfunction and organ inflammation. Management: Fatigue is often managed and improved by treating the underlying disorder (SLE) with immune modulating agents. Additionally, practising sleep hygiene such as going to bed and rising at approximately the same time each day as well as exercise may help. Arthritis in lupus is often managed with steroids, HCQ and methotrexate (MTX). The presence of IgG acL without a history of thrombosis requires no specific treatment; however, some clinicians advocate prophylactic treatment with HCQ for prevention of thromboses (4). We should note that IgG acL's carry the greatest risk of recurrent thrombosis.

Case 3. A 19 year-old African American male presents with several weeks of fatigue, malaise, alopecia, anorexia, diffuse weakness and fever (Tmax 103.8). Additionally, he has a 35 pound unintentional weight loss. On physical examination, he has painful nasal ulcers and decreased mental functioning. His chest radiograph reveals a left lower lobe infiltrate without atelectasis or effusion. Initial laboratories show lymphopenia, anemia, elevated liver associated enzymes, a creatine phosphate kinase (CPK) of 30,000 U/L (normal 55–170 U/L) and aldolase 20 U/L (normal 1.0–3.5 U/L. The ANA is 1:1280 and dsDNA 1:10. Antibodies to Sm antigen and U1-RNP are also positive. Additional evaluation shows a low complement C3, positive IgG Coomb's test, reticulocyte count of 4.5% (normal 0.5–1.5%), hematocrit of 33% (normal 41–51%) and ESR 56 mm/hr (normal 0–15). It is clear that this patient is presenting with SLE. He has systemic inflammatory disease involving multiple organs (namely the lung, muscle, kidney, mucous membranes, liver and CNS) that is associated with autoantibody formation. He also meets many of the ACR classification criteria. A pneumonic that is sometimes helpful to remember these criteria is RASH ON MAIDS. R for renal disorder, A for arthritis, S for serositis, H for hematological disorder, O for oral ulcers, N for neurological disorder, M for malar rash, A for antinuclear antibody, I for immunological disorder, D for discoid rash and S for sun sensitivity. Therapy: This patient was initially started on high dose steroids, MTX and intravenous immune globulin (IVIG) with a rapid improvement in his symptoms.

Case 4. A 60-year-old male is referred to you with arthritis, fatigue, fever (101F) and dyspnea. His past medical history is significant for coronary artery disease and cardiac arrhythmias. His current medications include aspirin, simvastatin and procainamide. A chest radiograph is performed and reveals blunting at the left costophrenic angle. An ANA is performed and is positive at 1:320. Does this patient have lupus? A closer look at this patient reveals that he does not have SLE but in fact has drug-induced lupus (DIL). The clinical features in DIL are less severe than idiopathic SLE and usually include constitutional symptoms such as fever, as well as arthritis and serositis. CNS involvement and renal manifestations are distinctly unusual in DIL. Other distinguishing features from SLE are an equal male to female prevalence and normal complement levels. Drugs that have a definite association with DIL are listed in Table 2 (5). Which serologic test would be least helpful in distinguishing SLE from DIL? The answer is anti-histone antibodies since they may be positive in both SLE and DIL. In DIL, anti-histone antibodies are positive more than 95% of the time, and in SLE they are positive in 70% of patients. Complement levels, urinalysis and dsDNA antibodies are all helpful in distinguishing SLE from DIL since they may be positive or abnormal in SLE but not in DIL. The prevalence of other autoantibodies in idiopathic SLE is as follows: dsDNA 40%, Smith 30%, nuclear RNP 30%, SS-A 35% and SS-B 15%. None of these later antibodies are present in DIL. How is DIL treated? First, discontinue the offending medication; a short course of NSAID or prednisone may also be needed. Can DIL related medications be used in patients with SLE? In general, we try to avoid these medications in lupus patients as they may precipitate a flare of disease or complicate the overall clinical picture.

Table 2. Drugs with good evidence of association with drug-induced lupus

Carbamazepine	Minocycline
Chlorpromazine	Penicillamine
Ethosuximide	Phenytoin
Hydralazine	Procainamide
Isoniazid	Quinidine
Methyldopa	Sulfasalazine

TREATMENT PARADIGMS FOR SLE

Let's now review some treatment paradigms for SLE. First, therapy is directed by the degree and severity of clinical manifestations. For example, skin disease may be responsive to HCQ alone, while more severe disease that involves multiple organs will require additional and more potent medications. Additionally, we must consider the risk to benefit ratio of our chosen therapy when treating this chronic disease. Acetaminophen, NSAIDS, HCQ and dihydroepiandrosterone (DHEA) are all relatively mild medications with relatively few side effects compared to other drugs used in SLE. MTX and steroids are used for more serious disease manifestations and have the potential for more serious side effects. Cyclosporin A, azathioprine and cyclophosphamide are used for very ill patients as are anti-biologic agents. Other things to consider when treating patients with SLE include avoidance of sulfur drugs, sun exposure and high estrogen containing oral contraceptive agents as all of these may precipitate a SLE flare. We also need to consider that our treatment itself can lead to disease and possibly even death in our lupus patients, most commonly secondary to infections. Other common causes of death in SLE are nephritis, renal failure or its complications, cardiovascular disease and CNS lupus.

CONCLUSIONS

In summary, the purpose of this review was to appreciate the complexity and the spectrum of the disease we name SLE and to appreciate the variety of ways it may present itself. A diagnosis of lupus requires longitudinal and careful follow-up as well as complete exploration of the immune system. Finally, treatment of SLE is always based on the degree and the severity of the clinical manifestations.

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SUMMARY

Systemic *lupus erythematosus* (SLE) is a systemic autoimmune disease characterized by autoantibody and immune complex formation which results in multi-organ inflammation. SLE is a heterogeneous disorder with a wide variety of presentations. It is important to understand the difference between classification and diagnostic criteria and how they apply to making a diagnosis of SLE in an individual patient. Classification criteria for a given disease select those clinical findings which both identify the disease and separate it from other patients who are ill. As a result, classification criteria do not include the full spectrum of manifestations of a disease. In our everyday clinical practices, we often use classification criteria as a reference, not as an absolute set of criteria that must be met for a patient to be diagnosed with lupus. For better understanding the difference between classification and diagnostic criteria we will now review some specific cases and the application of specific laboratory testing that we currently have available.

Toczeń rumieniowaty układowy – przypadki chorobowe

Toczeń rumieniowaty układowy (SLE) jest systemową chorobą autoimmunologiczną, charakteryzującą się tworzeniem w organizmie autoprzeciwciał i formowaniem kompleksów immunologicznych, których obecność w krążeniu prowadzi do procesu zapalnego, obejmującego liczne narządy. SLE jest schorzeniem heterogennym o bardzo szerokim wachlarzu prezentacji klinicznych choroby. W procesie rozpoznawania choroby bardzo istotne jest rozróżnienie kryteriów klasyfikacyjnych choroby od kryteriów diagnostycznych oraz umiejętność ich zastosowania w stawianiu diagnozy u chorych. Kryteria klasyfikacyjne choroby wydzielają te kliniczne objawy choroby, które zarówno identyfikują chorobę, jak i pozwalają wydzielić grupę od innych chorych na układowe choroby tkanki łącznej. W rezultacie kryteria klasyfikacyjne nie zawierają pełnego spektrum objawów występujących w chorobie. W codziennej praktyce klinicznej często używamy kryteriów klasyfikacyjnych jako referencyjnych, ale niekoniecznie stwierdzanych u chorego, u którego rozpoznajemy toczeń. Celem lepszego zrozumienia różnic między kryteriami klasyfikacyjnymi i diagnostycznymi choroby prezentujemy przypadki obrazujące poszczególne sytuacje kliniczne.