Clinical manifestations and diagnosis of systemic lupus erythematosus in adults

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause that can affect virtually any organ of the body. Immunologic abnormalities, especially the production of a number of antinuclear antibodies (ANA), are a prominent feature of the disease.

Patients present with variable clinical features ranging from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement. The clinical heterogeneity of SLE and the lack of pathognomonic features or tests pose a diagnostic challenge for the clinician. To complicate matters, patients may present with only a few clinical features of SLE, which can resemble other autoimmune, infectious, or hematologic diseases.

The diagnosis of SLE is generally based on clinical and laboratory findings after excluding alternative diagnoses. In the absence of SLE diagnostic criteria, SLE classification criteria are often used by clinicians as guidance to help identify some of the salient clinical features when making the diagnosis. Serologic findings are important in suggesting the possibility of SLE, with some antibodies (eg, anti-double-stranded DNA [anti-dsDNA] and anti-Smith [anti-Sm]) highly associated with this condition.

The clinical manifestations and an approach to the diagnosis of SLE will be reviewed here. Separate topic reviews related to SLE in adults include the following:

- (See "Overview of the management and prognosis of systemic lupus erythematosus in adults".)
- (See "Epidemiology and pathogenesis of systemic lupus erythematosus".)
- (See "Overview of cutaneous lupus erythematosus".)
- (See "Musculoskeletal manifestations of systemic lupus erythematosus".)
- (See "Diagnosis and classification of renal disease in systemic lupus erythematosus".)
- (See "Clinical features and therapy of lupus membranous nephropathy".)
- (See "Treatment and prognosis of diffuse or focal proliferative lupus nephritis".)
- (See "Indications for renal biopsy in patients with lupus nephritis".)
- (See "Hematologic manifestations of systemic lupus erythematosus".)
- (See "Gastrointestinal manifestations of systemic lupus erythematosus".)
- (See "Coronary heart disease in systemic lupus erythematosus".)
- (See "Non-coronary cardiac manifestations of systemic lupus erythematosus in adults".)
- (See "Diagnostic approach to the neuropsychiatric manifestations of systemic lupus erythematosus".)
- (See "Neurologic manifestations of systemic lupus erythematosus".)
- (See "Approach to contraception in women with systemic lupus erythematosus".)
- (See "Pregnancy in women with systemic lupus erythematosus".)
- (See "Drug-induced lupus".)

CLINICAL MANIFESTATIONS

Major clinical features and organ involvement

Constitutional symptoms — Constitutional symptoms such as fatigue, fever, and weight loss are present in most patients with systemic lupus erythematosus (SLE) at some point during the course of the disease.

- **Fatigue** – Fatigue is the most common complaint, occurring in 80 to 100 percent of patients, and can sometimes be disabling. Its presence is not clearly correlated with other measures of disease activity and is more frequently associated with depression, sleep disturbances, and concomitant fibromyalgia [1-5].

- **Fever** – Fever can be a manifestation of active disease and is seen in over 50 percent of patients with SLE [6]. However, in clinical practice, distinguishing fever associated with a lupus flare from other causes of fever, such as infection, a drug reaction, or malignancy,

can be difficult. Clinically, there are no specific features that definitively distinguish fever due to SLE from fever due to other causes. The history may be helpful in determining the cause of the fever. As an example, fever in the setting of moderate or high doses of glucocorticoids should lead one to strongly suspect new infection, particularly if other signs of active disease are not present. Fever that does not respond to nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, and/or low to moderate doses of glucocorticoids should raise the suspicion of an infectious or drug-related etiology, since most fevers due to active SLE will remit with use of these agents [7]. In addition, a low white blood cell (WBC) count in the setting of fever would be more consistent with lupus activity rather than infection.

Serious infections are a major cause of morbidity among patients and should be considered in all immunocompromised SLE patients with fever. (See 'Clinical manifestations' above.)

- **Myalgia** – Myalgia is also common among patients with SLE, whereas severe muscle weakness or myositis is relatively uncommon. Myalgia and muscle weakness are discussed in more detail separately. (See "Musculoskeletal manifestations of systemic lupus erythematosus", section on 'Muscle disease'.)

- **Weight change** – Weight changes are frequent in patients with SLE and may be related to the disease or to its treatment. Weight loss often occurs prior to the diagnosis of SLE. Unintentional weight loss may be due to decreased appetite, side effects of medications (particularly diuretics and occasionally hydroxychloroquine), and gastrointestinal disease (eg, gastroesophageal reflux, abdominal pain, peptic ulcer disease, or pancreatitis) (see "Gastrointestinal manifestations of systemic lupus erythematosus"). Weight gain in SLE may be due to salt and water retention associated with hypoalbuminemia (eg, due to nephrotic syndrome or protein-losing enteropathy) or, alternatively, due to increased appetite associated with the use of glucocorticoids. (See "Overview of heavy proteinuria and the nephrotic syndrome" and "Gastrointestinal manifestations of systemic lupus erythematosus", section on 'Protein-losing enteropathy'.)

Arthritis and arthralgias — Arthritis and arthralgias occur in over 90 percent of patients with SLE and are often one of the earliest manifestations [8]. Arthritis, with demonstrable inflammation, occurs in 65 to 70 percent of patients and tends to be migratory, polyarticular, and symmetrical. The arthritis is moderately painful, usually does not cause erosion, and is rarely

deforming (picture 1A-B). However, occasionally patients with SLE also develop a deforming erosive arthritis, which is similar to that of rheumatoid arthritis (RA) [9]. The clinical characteristics and management of arthritis and arthralgias in SLE are discussed in detail elsewhere. (See "Musculoskeletal manifestations of systemic lupus erythematosus", section on 'Arthritis and arthralgias'.)

Mucocutaneous involvement — Most patients develop skin and mucous membrane lesions at some point during the course of their disease. There is tremendous variability in the type of skin involvement in SLE. The most common lesion is a facial eruption that characterizes acute cutaneous lupus erythema (also known as "the butterfly rash") that presents as erythema in a malar distribution over the cheeks and nose (but sparing the nasolabial folds) that appears after sun exposure (picture 2A-B). Some patients may develop discoid lesions, which are more inflammatory and which have a tendency to scar (picture 3A-B). Photosensitivity is also a common theme for skin lesions associated with SLE. The various cutaneous manifestations of SLE are presented in detail separately. (See "Overview of cutaneous lupus erythematosus".)

Many patients develop oral and/or nasal ulcers, which are usually painless in contrast to herpetic chancre blisters. Nasal ulcers may lead to nasal septal perforation. Nonscarring alopecia is also observed in many SLE patients at some point during the course of their disease. Scarring alopecia can occur in patients with discoid lupus erythematosus. (See "Overview of cutaneous lupus erythematosus", section on 'Discoid lupus erythematosus'.)

Cardiac involvement and vascular manifestations — A variety of cardiac and vascular abnormalities can occur in patients with SLE.

- Cardiac disease among patients with SLE is common and can involve the pericardium, myocardium, valves, conduction system, and coronary arteries. Pericarditis, with or without an effusion, is the most common cardiac manifestation of SLE, occurring in approximately 25 percent of patients at some point during their disease course [10]. Verrucous (Libman-Sacks) endocarditis is usually clinically silent, but it can produce valvular insufficiency and can serve as a source of emboli (picture 4). Myocarditis is uncommon but may be severe. Patients with SLE also have an increased risk of coronary artery disease. (See "Non-coronary cardiac manifestations of systemic lupus erythematosus in adults" and "Coronary heart disease in systemic lupus erythematosus".)

  Neonatal lupus, which can occur in babies of women with SLE expressing anti-Ro/SSA and anti-La/SSB, can cause heart block of varying degrees that may be noted in utero and/or

that may present as congenital heart block and is discussed separately. (See "Neonatal lupus: Epidemiology, pathogenesis, clinical manifestations, and diagnosis".)

- **Raynaud phenomenon** – Raynaud phenomenon in SLE is a vasospastic process induced by cold that occurs in up to 50 percent of patients with SLE (picture 5) [6]. Raynaud phenomenon is characterized by intermittent acral pallor followed by cyanosis and erythroderma [11]. Raynaud phenomenon is discussed in detail separately. (See "Clinical manifestations and diagnosis of Raynaud phenomenon".)

- **Vasculitis** – Estimates of the prevalence of vasculitis among SLE patients from large cohorts range from 11 to 36 percent [12]. The clinical spectrum of vasculitis in the setting of SLE is broad due to the potential for inflammatory involvement of vessels of all sizes. Small vessel involvement is the most common, often manifesting as cutaneous lesions; however, medium- and large-vessel involvement have also been observed. Cutaneous small-vessel vasculitis can manifest as palpable purpura, petechiae, papulonodular lesions, livedo reticularis, panniculitis, splinter hemorrhages, and superficial ulcerations (see "Evaluation of adults with cutaneous lesions of vasculitis"). As an example, a large series of 670 SLE patients identified vasculitis among 11 percent of patients [13]. Cutaneous lesions were the main clinical presentation of vasculitis, present in 89 percent of patients. The remaining 11 percent of patients with vasculitis had visceral involvement (eg, peripheral nerves, lung, pancreas, and kidney).

  Other specific types of vasculitic involvement in SLE include mesenteric vasculitis, hepatic vasculitis, pancreatic vasculitis, coronary vasculitis, pulmonary vasculitis, and retinal vasculitis, as well as vasculitis of the peripheral or central nervous system. A few cases of aortitis, similar to that seen in Takayasu arteritis, have been reported [14]. (See "Overview of cutaneous lupus erythematosus" and "Gastrointestinal manifestations of systemic lupus erythematosus", section on 'Autoimmune hepatitis' and "Gastrointestinal manifestations of systemic lupus erythematosus", section on 'Acute pancreatitis' and "Gastrointestinal manifestations of systemic lupus erythematosus", section on 'Mesenteric vasculitis/ischemia' and "Neurologic manifestations of systemic lupus erythematosus" and "Retinal vasculitis associated with systemic disorders and infections", section on 'Systemic immune-mediated causes'.)

- **Thromboembolic disease** – Thromboembolic disease can complicate SLE, particularly in the context of antiphospholipid antibodies. Although the precise mechanism is unknown,

thromboembolic disease can affect both the venous and arterial circulations [15,16]. As an example, in a large observational cohort of 554 newly diagnosed SLE patients followed for a median of 6.3 years, an arterial thrombotic event (ATE) occurred in 11 percent, a venous thrombotic event (VTE) occurred in 5 percent, and the estimated 10-year risks were 10 percent for VTE, 26 percent for ATE, and 33 percent for any thrombotic event [16]. Antimalarials may be protective for the development of thromboembolic disease in SLE [17].

Renal involvement — Renal involvement is clinically apparent in approximately 50 percent of SLE patients and is a significant cause of morbidity and mortality [18]. Thus, periodic screening for the presence of lupus nephritis with urinalyses, quantitation of proteinuria, and estimation of the glomerular filtration rate is an important component of the ongoing management of SLE patients. Several forms of glomerulonephritis can occur, and renal biopsy is useful to define the type and extent of renal involvement. The clinical presentation of lupus nephritis is highly variable, ranging from asymptomatic hematuria and/or proteinuria to nephrotic syndrome and rapidly progressive glomerulonephritis with loss of renal function. Some patients with lupus nephritis also have hypertension. (See "Diagnosis and classification of renal disease in systemic lupus erythematosus".)

Gastrointestinal involvement — Gastrointestinal symptoms are common in SLE patients, occurring in up to 40 percent of patients. The majority of gastrointestinal symptoms are caused by adverse medication reactions and viral or bacterial infections [19]. SLE-related gastrointestinal abnormalities can involve almost any organ along the gastrointestinal tract and include esophagitis, intestinal pseudo-obstruction, protein-losing enteropathy, lupus hepatitis, acute pancreatitis, mesenteric vasculitis or ischemia, and peritonitis. The gastrointestinal manifestations of SLE are discussed in detail elsewhere. (See "Gastrointestinal manifestations of systemic lupus erythematosus".)

Pulmonary involvement — During the course of their disease, many patients develop symptoms secondary to pulmonary involvement of SLE. Pulmonary manifestations of SLE include pleuritis (with or without effusion), pneumonitis, interstitial lung disease, pulmonary hypertension, shrinking lung syndrome, and alveolar hemorrhage. Respiratory symptoms must also be distinguished from infection, particularly in patients on immunosuppressive therapy. The risk of thromboembolic involvement is increased in those with antiphospholipid antibodies or with lupus anticoagulant. (See "Pulmonary manifestations of systemic lupus erythematosus in adults".)

Neuropsychiatric involvement — Neuropsychiatric involvement of SLE consists of a broad range of neurologic and psychiatric manifestations, including cognitive dysfunction, organic brain syndromes, delirium, psychosis, seizures, headache, and/or peripheral neuropathies. Other less common problems are movement disorders, cranial neuropathies, myelitis, and meningitis. (See "Neurologic manifestations of systemic lupus erythematosus".)

Psychosis, which may be due to SLE or to glucocorticoid treatment, is one of several psychiatric manifestations of SLE. Others include depression, anxiety, and mania. (See "Neuropsychiatric manifestations of systemic lupus erythematosus".)

Thromboembolic events, often in association with antiphospholipid antibodies or with lupus anticoagulant, may occur in a substantial minority (20 percent) of patients with SLE [20]. Arterial thromboemboli may cause focal neurologic problems, such as stroke or seizures and/or more diffuse cognitive defects [20]. (See "Clinical manifestations of antiphospholipid syndrome".)

Hematologic abnormalities — Hematologic abnormalities are common in SLE, and all three blood cell lines can be affected. Anemia of chronic disease is the most common type of anemia among patients with SLE. Leukopenia is common in SLE patients, occurring in approximately 50 percent of patients [21]. Leukopenia can be due to lymphopenia and/or secondary neutropenia and generally correlates with clinically active disease. Neutropenia may also result from toxicity due to immunosuppressive medications. Mild thrombocytopenia is also a common hematologic abnormality. Rarely, severe thrombocytopenia can occur and requires treatment. Autoimmune hemolytic anemia is also relatively rare but can be severe, requiring immediate therapy. A more detailed discussion of the hematologic manifestations of SLE is presented separately. (See "Hematologic manifestations of systemic lupus erythematosus".)

Lymph node enlargement commonly occurs in association with active SLE and usually involves the cervical, axillary, and inguinal regions. Splenomegaly can also be observed among SLE patients, particularly with active disease. (See "Hematologic manifestations of systemic lupus erythematosus", section on 'Lymphadenopathy, splenomegaly, and high blood cell counts'.)

Ophthalmologic involvement — Any structure of the eye can be involved in SLE, with keratoconjunctivitis sicca being the most common manifestation as a result of secondary Sjögren's syndrome [22] (see "Clinical manifestations of Sjögren's syndrome: Exocrine gland disease"). The next most common pathologic condition involving the eye in lupus patients is retinal vasculopathy in the form of cotton wool spots. (See "Retinal vasculitis associated with systemic disorders and infections", section on 'Systemic immune-mediated causes'.)

Other less common ophthalmologic manifestations of SLE include optic neuropathy, choroidopathy, episcleritis, scleritis, and anterior uveitis (iritis, iridocyclitis). (See "Optic neuropathies", section on 'Systemic autoimmune disease' and "Episcleritis" and "Clinical manifestations and diagnosis of scleritis" and "Uveitis: Etiology, clinical manifestations, and diagnosis", section on 'Systemic inflammatory diseases'.)

Orbital tissues such as the lacrimal gland (typically resulting in sicca), extraocular muscles, and other orbital tissues may also be involved in SLE, leading to pain, proptosis, lid swelling, and diplopia [23]. In addition, there are specific ocular toxicities secondary to medications seen in patients with SLE, including glucocorticoid-induced glaucoma and retinal toxicity due to antimalarial therapy.

Other associated conditions and complications — A number of comorbid medical conditions that are related to either the underlying disease or therapy can occur in patients with SLE.

- **Immunodeficiencies** – Hereditary angioedema is a rare genetic disorder primarily caused by a defect in the C1 inhibitor. It can be associated with some inflammatory and autoimmune disorders, including SLE [24]. (See "Hereditary angioedema: Pathogenesis and diagnosis".)

  Patients with other forms of complement deficiency like C2 also have forms of SLE. Often the manifestations depend on whether such deficiencies are homozygous. Patients with complete C4 deficiency and C1q deficiency often present with SLE [25]. Inherited C4 deficiency is discussed in detail separately. (See "Inherited disorders of the complement system", section on 'C4 deficiency'.)

- **Antiphospholipid syndrome** – Antiphospholipid antibodies are detected in 40 percent of patients with SLE [26]. However, the development of antiphospholipid syndrome is much less common. (See "Diagnosis of antiphospholipid syndrome" and "Clinical manifestations of antiphospholipid syndrome".)

- **Fibromyalgia** – Patients with SLE, as well as several other systemic rheumatic diseases, have a higher prevalence of fibromyalgia than the general population [27]. (See "Musculoskeletal manifestations of systemic lupus erythematosus", section on 'Fibromyalgia'.)

- **Osteonecrosis** – The estimated risk of osteonecrosis, which can present with severe joint pain among patients with SLE, varies widely, ranging from 3 to 40 percent [28]. The

increased risk is thought to be related to the underlying disease as well as the concomitant use of glucocorticoids. (See "Musculoskeletal manifestations of systemic lupus erythematosus", section on 'Osteonecrosis'.)

- **Osteoporosis** – Osteoporosis is a common complication of SLE and is discussed in detail separately. (See "Musculoskeletal manifestations of systemic lupus erythematosus", section on 'Osteoporosis'.)

- **Infection** – Serious infectious complications, especially of the skin, respiratory, and urinary systems, develop in up to 50 percent of SLE patients [6,29-32]. A large cohort from a Medicaid database of 33,565 SLE patients, 7113 of whom had lupus nephritis, found that the incidence rate (per 100 person-years) of serious infections requiring hospitalization was 10.8 in the SLE cohort and 23.9 in the lupus nephritis subcohort [33]. A large majority of infections (approximately 80 percent) are due to pathogenic bacteria [32]. Opportunistic infections, including those due to fungi, can be related to the use of immunosuppressive therapy and are a common cause of death [34-37]. Consequently, ascribing fever to SLE in an immunocompromised patient should be done only after reasonable efforts have been made to exclude infection.

  Risk factors for infection include active SLE disease, long-term disease damage, neutropenia, lymphopenia, hypocomplementemia, renal involvement, neuropsychiatric manifestations, and the use of glucocorticoids and other immunosuppressive drugs [32]. Male gender and black race have also been shown to be risk factors for infection, while antimalarials have been found to be protective [33]. Viral infections are also common, including parvovirus B19 (which can cause a lupus-like syndrome), Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, and human papillomavirus. Mycobacterial infections, including non-tuberculosis, have been noted to be more frequent in patients with SLE [29,32].

- **Other autoimmune diseases** – There is an increased prevalence of thyroid disease among patients with SLE, usually in the form of Hashimoto's thyroiditis. Myasthenia gravis has also been reported to co-occur in patients with SLE. There is a high prevalence of autoimmune diseases among families of patients with SLE [38-40]. (See "Thyroid disorders and connective tissue disease", section on 'Systemic lupus erythematosus' and "Clinical manifestations of myasthenia gravis", section on 'Epidemiology'.)

EVALUATION

When to suspect SLE — The initial diagnosis of systemic lupus erythematosus (SLE) depends on the manner of presentation and the exclusion of alternative diagnoses. Given the heterogeneity of clinical presentations, there are some patients for whom the constellation of presenting clinical features and supportive laboratory studies makes the diagnosis of SLE relatively straightforward. By contrast, there are others who present with isolated complaints or infrequent disease characteristics and represent more of a diagnostic challenge. Demographics should also be taken into account when evaluating a patient for SLE, since it occurs primarily in young women of childbearing age. In addition, SLE occurs more commonly in certain racial and ethnic groups, particularly black, Asian, and Hispanic patients compared with white patients [41]. (See "Epidemiology and pathogenesis of systemic lupus erythematosus", section on 'Epidemiology'.)

As an example, the diagnosis of SLE is more likely to be present in a young woman who develops fatigue, arthralgia, and pleuritic chest pain and is found to have hypertension, a malar rash, a pleural friction rub, several tender and swollen joints, and mild peripheral edema. Laboratory testing may reveal leukopenia, anemia, an elevated serum creatinine, hypoalbuminemia, proteinuria, an active urinary sediment, hypocomplementemia, and positive tests for antinuclear antibodies (ANA), including those to double-stranded DNA (dsDNA) and the Smith (Sm) antigen. By contrast, another patient may present with fatigue and arthralgias without evidence of organ involvement in the setting of a positive ANA test. Such patients may or may not subsequently develop characteristic multisystem features of SLE in the following months or years. (See 'Clinical manifestations' above.)

Thus, the initial evaluation requires a careful history and physical exam, along with selected laboratory testing to identify features that are characteristic of SLE or that suggest an alternative diagnosis. Patients presenting with symptoms for a shorter duration of time will need close follow-up, as the frequency with which various features of SLE are observed differs according to stage of disease [42-46].

History and physical examination — We perform a thorough medical history, with particular attention to the following symptoms and signs:

- Constitutional symptoms, such as fever, fatigue, lymphadenopathy, or weight loss
- Photosensitive skin lesions, such as a malar rash

- Painless oral or nasal ulcers
- Hair loss that is patchy or frontal/peripheral
- Raynaud phenomenon
- Joint pain or swelling, which can be migratory or symmetrical
- Dyspnea or pleuritic chest pain suggestive of serositis
- Chest pain suggestive of pericarditis
- Lower-extremity edema
- Neurologic symptoms, such as seizures or psychosis
- Recurrent miscarriages (see "Pregnancy in women with systemic lupus erythematosus")
- Exposure to medications associated with drug-induced lupus (see "Drug-induced lupus")

Given the broad range of clinical manifestations of SLE, it is helpful to consider the various features according to frequency at disease onset (table 1).

A complete physical examination is indicated, since any organ system can be involved in SLE. Pertinent physical examination findings include the following:

- Skin lesions consistent with a malar rash or discoid lesions
- Scarring or nonscarring patchy alopecia
- Oral or nasopharyngeal ulcers
- Polyarticular arthritis, which is often symmetric
- Subluxation at the metacarpophalangeal joints and rheumatoid-like swan neck deformities in the hands
- Decreased or abnormal breath sounds that may indicate a pleural effusion, pneumonitis, or interstitial lung disease
- Lower-extremity edema and hypertension

Laboratory testing — We obtain the following routine laboratory tests, which may provide diagnostically useful information:

- Complete blood count and differential may reveal leukopenia, mild anemia, and/or thrombocytopenia
- Elevated serum creatinine may be suggestive of renal dysfunction
- Urinalysis with urine sediment may reveal hematuria, pyuria, proteinuria, and/or cellular casts
- Serum protein electrophoresis may demonstrate a hypergammaglobulinemia that is suggestive of a systemic inflammatory process

In addition to the routine laboratories described above, we perform the following laboratory tests, which support the diagnosis of SLE if abnormal:

- ANA (ideally by indirect immunofluorescence testing)
- Anti-double-stranded DNA (anti-dsDNA)
- Antiphospholipid antibodies (lupus anticoagulant [LA], immunoglobulin [Ig] G and IgM anticardiolipin [aCL] antibodies, and IgG and IgM anti-beta2-glycoprotein [GP] 1)
- C3 and C4 or CH50 complement levels
- Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels
- Urine protein-to-creatinine ratio

The ANA test is positive in virtually all patients with SLE at some time in the course of their disease (see "Measurement and clinical significance of antinuclear antibodies"). If the ANA is positive, one should test for other specific antibodies, such as anti-dsDNA, anti-Smith (anti-Sm), Ro/SSA, La/SSB, and U1 ribonucleoprotein (RNP), which are described further below. In some labs, a positive ANA test by indirect immunofluorescence will automatically result in testing for such additional ANA that are often present in patients with SLE. However, a positive ANA must also be interpreted in the setting of other clinical and laboratory findings. Almost 15 percent of the population in the United States has been found to have a positive ANA of at least 1:80 by indirect immunofluorescence, but only 10 percent have a true autoimmune disorder [47]. A more detailed discussion related to measurement and interpretation of ANA testing can be found elsewhere. (See "Measurement and clinical significance of antinuclear antibodies".)

- Anti-dsDNA and anti-Sm antibodies are highly specific for SLE, but anti-Sm antibodies lack sensitivity [48,49]. Anti-dsDNA and anti-Sm antibodies are seen in approximately 70 and 30 percent of patients with SLE, respectively. (See "Antibodies to double-stranded (ds)DNA, Sm, and U1 RNP".)

- Anti-Ro/SSA and anti-La/SSB antibodies are present in approximately 30 and 20 percent of patients with SLE, respectively; however, both antibodies are more commonly associated with Sjögren's syndrome [48]. (See "The anti-Ro/SSA and anti-La/SSB antigen-antibody systems".)

- Anti-U1 RNP antibodies are observed in approximately 25 percent of patients with SLE, but they also occur in patients with other conditions, and high levels are almost always present in patients with mixed connective tissue disease (MCTD) [48,49]. (See "Antibodies to double-stranded (ds)DNA, Sm, and U1 RNP".)

- Antiribosomal P protein antibodies have a high specificity for SLE but low sensitivity for SLE. They also lack specificity for involvement of a particular organ system or disease manifestation. (See "Antiribosomal P protein antibodies", section on 'Clinical utility of antiribosomal P antibodies'.)

If the initial ANA test is negative but the clinical suspicion of SLE is high, then additional antibody testing may still be appropriate. This is partly related to the differences in the sensitivity and specificity among the methods used to detect ANA. A more detailed discussion on the techniques used to detect ANA and the reasons behind some of the variability in test results is presented separately. (See "Measurement and clinical significance of antinuclear antibodies", section on 'Advantages and disadvantages of methods to detect ANA' and 'ANA-negative lupus' below.)

We perform the following additional laboratory tests in selected patients:

- **Rheumatoid factor and anti-cyclic citrullinated peptide antibodies** – In patients with predominant arthralgias or arthritis, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies may help exclude a diagnosis of rheumatoid arthritis (RA). RF has less diagnostic utility, since 20 to 30 percent of people with SLE have a positive RF. Anti-CCP antibodies, however, have a much higher specificity for RA and may be more useful for distinguishing the arthritis associated with RA. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Rheumatoid factors' and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

- **Serologic studies for infection** – In patients with a brief history (eg, less than six weeks) of predominant arthralgias or arthritis, we perform serologic testing for human parvovirus B19. We also perform serologic testing for hepatitis B virus and hepatitis C virus in patients with multisystemic clinical findings. In areas endemic for Lyme disease, we may send serologic studies for *Borrelia* as well. Testing for Epstein-Barr virus infection may also be indicated in the appropriate clinical setting. (See "Diagnosis and differential diagnosis of rheumatoid arthritis", section on 'Viral polyarthritis' and "Viruses that cause arthritis" and "Diagnosis of Lyme disease".)

- **Creatine kinase** – An elevated creatine kinase (CK) may reflect myositis, which is relatively uncommon in patients with SLE. Myositis may also suggest an alternative diagnosis, such as MCTD, polymyositis, or dermatomyositis.

- **24-hour urine collection** – If the spot urine protein-to-creatinine ratio is above 0.05 g/mmol, then a 24-hour urine collection should be performed, as the spot urine collection may not reflect the true amount of proteinuria [50]. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults", section on '24-hour versus spot urine collection'.)

Additional testing in selected patients — Biopsy of an involved organ (eg, skin or kidney) is necessary in some cases. Typical histologic findings in various organs in SLE are discussed in topic reviews devoted to the particular sites of involvement. (See "Indications for renal biopsy in patients with lupus nephritis" and "Diagnosis and classification of renal disease in systemic lupus erythematosus" and "Overview of cutaneous lupus erythematosus".)

Other tests that may be necessary are typically dictated by the clinical presentation and associated differential diagnostic possibilities. Examples include:

- Electrocardiography in the assessment of chest pain that may be due to pericarditis or to myocardial ischemia
- Tests to assess for pulmonary embolism in a patient with pleuritic chest pain and dyspnea
- Diffusing capacity for carbon monoxide to assess for suspected pulmonary hemorrhage and to estimate the severity of interstitial lung disease

Diagnostic imaging may be valuable but is not routinely obtained unless indicated by the presence of symptoms, clinical findings, or laboratory abnormalities. Examples include:

- Plain radiographs (eg, of swollen joints; unlike affected joints in RA, erosions are observed infrequently in SLE [51]).

- Musculoskeletal ultrasonography (eg, of painful joints to detect synovitis and tenosynovitis in the hands and wrists [52,53]).

- Renal ultrasonography (eg, to assess kidney size and to rule out urinary tract obstruction when there is evidence of renal impairment).

- Chest radiography (eg, for suspected pleural effusion, interstitial lung disease, cardiomegaly).

- Echocardiography (eg, for suspected pericardial involvement, to assess for a source of emboli, or noninvasive estimation of pulmonary artery pressure; and for evaluation of

suspected valvular lesions, such as verrucae).

- Computed tomography (CT; eg, for abdominal pain, suspected pancreatitis, interstitial lung disease).

- Magnetic resonance imaging (MRI; eg, for focal neurologic deficits or cognitive dysfunction).

CLASSIFICATION CRITERIA

Several classification criteria have been developed for systemic lupus erythematosus (SLE) as a means of categorizing patients for inclusion in research studies. These criteria can be useful for clinicians in systematically documenting key disease features, but their imperfect sensitivity and specificity limit their use for diagnostic purposes.

- **2019 EULAR/ACR criteria** – The European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE were developed to improve detection of early- or new-onset SLE as well as improve the sensitivity and specificity compared with previous criteria (table 2A-B) [54,55]. The classification for SLE requires the presence of a positive antinuclear antibodies (ANA) as an entry criterion. Additive criteria consist of seven clinical (ie, constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal) and three immunologic (ie, antiphospholipid antibodies, complement proteins, SLE-specific antibodies) categories, each of which are weighted from 2 to 10. Patients are classified as having SLE with a score of 10 or more points. In the validation cohort, which included patients with early disease, the EULAR/ACR criteria had a sensitivity of 96.1 percent and a specificity of 93.4 percent, compared with the 96.7 percent sensitivity and 83.7 percent specificity of the Systemic Lupus International Collaborating Clinics (SLICC) criteria and the 82.8 percent sensitivity and 93.4 percent specificity of the ACR criteria.

- **2012 SLICC criteria** – In 2012, the SLICC proposed classification criteria that were developed to address inherent weaknesses of the 1997 ACR classification criteria (table 3) [56]. As an example, one of the major limitations of the 1997 ACR criteria is that patients with biopsy-confirmed lupus nephritis could still fail to fulfill criteria. Other concerns regarding the ACR criteria included the possible duplication of highly correlated cutaneous features (such as malar rash and photosensitivity), the lack of inclusion of other cutaneous

manifestations (such as maculopapular or polycyclic rash), and the omission of many neurologic manifestations of SLE (such as myelitis). The ACR criteria also did not include relevant immunologic information such as low serum levels of complement components.

Classification as having SLE by the SLICC criteria requires either that a patient satisfy at least 4 of 17 criteria, including at least 1 of the 11 clinical criteria and one of the six immunologic criteria, or that the patient has biopsy-proven nephritis compatible with SLE in the presence of ANA or anti-double-stranded DNA (anti-dsDNA) antibodies.

The SLICC criteria were validated by analysis of 690 patients with SLE or other rheumatic diseases. In this initial validation testing, the SLICC revised criteria had greater sensitivity but lower specificity than the 1997 ACR classification criteria (sensitivity of 97 versus 83 percent and specificity of 84 versus 96 percent, respectively).

Despite the improved sensitivity compared with the ACR criteria, the SLICC criteria might delay the diagnosis of SLE in a significant number of patients, and some patients might not be classified at all. These situations were demonstrated in a study in which patients with SLE from two large cohorts 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 [57]. Among the patients diagnosed later with the SLICC criteria, in the majority of cases, the delay was due to the fact that the combination of malar rash and photosensitivity both fall within the acute cutaneous SLE category and thus only count as one criterion.

- **1997 ACR criteria** – The classification criteria that were developed by the American Rheumatism Association (ARA, now the ACR) for the classification of SLE were established by cluster analyses, primarily in academic centers and in Caucasian patients [58-60].

  The patient is classified with SLE using the ACR criteria if four or more of the manifestations are present, either serially or simultaneously, during any interval of observations (table 3) [58,59]. A positive lupus erythematosus cell test, used in older criteria, was replaced by the presence of antiphospholipid antibodies [58]. When tested against other rheumatic diseases, these criteria have a sensitivity and specificity of approximately 96 percent.

DIAGNOSIS

The diagnosis of systemic lupus erythematosus (SLE) is based upon the judgment of an experienced clinician who recognizes characteristic constellations of symptoms and signs in the setting of supportive serologic studies after excluding alternative diagnoses. This is often challenging due to the great variability in the expression of SLE. Although the classification criteria were designed for research purposes, many clinicians refer to aspects of these criteria when making the diagnosis of SLE. (See 'Classification criteria' above.)

In the absence of existing "diagnostic criteria," we describe our general approach to the diagnosis that takes into consideration the strengths of both the 1997 American College of Rheumatology (ACR) criteria or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria described above (table 3) (see 'Classification criteria' above). Over time, the way in which the 2019 European League Against Rheumatism (EULAR)/ACR classification criteria may fit into the diagnostic schema discussed below will become more clear.

Note that our general diagnostic approach does not adequately address the myriad manifestations or subtleties of some clinical features, nor does it substitute for clinical judgment. Thus, it is often appropriate to refer the patient in whom the diagnosis of SLE is suspected to a rheumatologist with experience in this disease [61].

Our diagnostic criteria

Definite SLE — After excluding alternative diagnoses, we diagnose SLE in the patient who fulfills the 1997 ACR criteria or the 2012 SLICC criteria (table 3). As previously mentioned, the ACR criteria require that a patient satisfy at least 4 of 11 criteria. The SLICC criteria require either that a patient satisfy at least 4 of 17 criteria, including at least 1 of the 11 clinical criteria and one of the six immunologic criteria, **or** that the patient has biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANA) or anti-double-stranded DNA (anti-dsDNA) antibodies. (See 'Classification criteria' above.)

Probable SLE — There are patients who do not fulfill the classification criteria for SLE but in whom we still diagnose the disorder. These patients include those presenting with an inadequate number of ACR or SLICC criteria or those who have other SLE manifestations not included in either classification criteria.

As a loose guide, we diagnose SLE in patients who have two or three of the ACR or SLICC

criteria, along with at least one other feature that may be associated with but is not specific for SLE. Some of these features include the following [62]:

- Optic neuritis, aseptic meningitis
- Glomerular hematuria
- Pneumonitis, pulmonary hemorrhage, pulmonary hypertension, interstitial lung disease
- Myocarditis, verrucous endocarditis (Libman-Sacks endocarditis)
- Abdominal vasculitis
- Raynaud phenomenon
- Elevated acute phase reactants (eg, erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP])

Possible SLE — We consider SLE a possible diagnosis in individuals who have only one of the ACR/SLICC criteria, in addition to at least one or two of the other features listed above. Other terms that have been used to describe patients with probable or possible SLE include incipient or latent lupus, which has been defined as patients who have three or fewer of the ACR or SLICC criteria [63].

In general, patients with either probable or possible SLE are managed similarly to patients with SLE and treated according to their predominant symptoms and manifestations. Over time, the symptoms in these patients may persist, evolve into definite SLE or a related connective tissue disorder, or even resolve. In addition, these patients may develop positive serology over time and become more clearly diagnosable as SLE. However, patients treated with high doses of prednisone may "lose" their antibodies, and it may be more difficult to diagnose the underlying disease.

Undifferentiated connective tissue disease — Other patients who have even fewer features suggestive of SLE may be classified as having undifferentiated connective tissue disease (UCTD). This term is used to describe patients with signs and symptoms suggestive of a systemic autoimmune disease but who do not meet the ACR criteria for SLE or another defined connective tissues disease [64]. (See "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes".)

Case series have been published that summarize the outcome of patients who have UCTD at presentation [65-69]. Up to one-third of patients have all symptoms and signs disappear over a 10-year follow-up period. Anywhere from 40 to 60 percent of patients continue to exhibit their initial clinical features, while 5 to 30 percent evolve and meet classification criteria for a definite

disease, such as SLE, rheumatoid arthritis, scleroderma, or an inflammatory myopathy (myositis) [65-69] (see "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes"). Thus, patients with UCTD should be followed carefully, encouraged to report new symptoms, and have periodic laboratory testing to assess for the emergence of new clinical features or laboratory findings. Appropriate testing should include the laboratory testing described above. (See 'Laboratory testing' above.)

ANA-negative lupus — ANA-negative SLE has been recognized since the 1970s but was later shown to be influenced by the testing methods used to detect ANA. At that time, it was estimated that about 5 percent of patients with SLE were ANA-negative by indirect immunofluorescence [70]. However, this negative finding occurred because sera were tested using rodent, not human, tissues as the substrate for the indirect immunofluorescence test for ANA [71]. By comparison, anti-Ro/SSA antibodies were found in many of these patients when a human cell line extract was used as the substrate for anti-Ro/SSA antibody testing.

The subsequent substitution of human epithelial type 2 (Hep-2) cells (a human cell line) for rodent tissue sections in the indirect immunofluorescence ANA assay has resulted in even fewer SLE patients with negative ANA by indirect immunofluorescence. Nevertheless, on rare occasions, the presence of anti-Ro/SSA antibodies may suggest a systemic autoimmune disease despite the presence of a negative ANA indirect immunofluorescence. As an example, in one study in Sweden, among 4025 sera tested for ANA, 64 patients with negative ANA by indirect immunofluorescence had anti-Ro/SSA antibodies [72]. Of these 64 patients, 12 had SLE and 5 had cutaneous lupus erythematosus.

The clinician should understand the technique used to detect the ANA, since this can influence the result. As an example, a negative ANA by indirect immunofluorescence is clinically useful as it dramatically decreases the likelihood of SLE. On the other hand, in a patient with a strong clinical suspicion for SLE and a negative ANA result by a solid-phase assay, the test should be repeated using indirect immunofluorescence method with Hep-2 cells, given the increased risk of a false-negative result for the initial ANA test by solid-phase assay. A detailed discussion of the methods used to detect ANA is presented separately. (See "Measurement and clinical significance of antinuclear antibodies".)

Other factors that may also influence ANA negativity in SLE patients include disease duration and treatment exposure [73]. In our experience, the frequency of ANA-negative SLE is lower in patients presenting at an early stage of their disease. In addition, SLE patients who have

longstanding disease and/or have undergone treatment may lose ANA reactivity and become serologically negative over time.

DIFFERENTIAL DIAGNOSIS

Given the protean manifestations of systemic lupus erythematosus (SLE), the differential diagnosis is correspondingly broad. While it is beyond the scope of this review to provide a comprehensive list of all possible alternative diagnoses, we present several here.

- **Rheumatoid arthritis** – Early rheumatoid arthritis (RA) may be difficult to distinguish from the arthritis of SLE, since both conditions cause joint tenderness and swelling (table 4). Features such as swan neck deformities, ulnar deviation, and soft tissue laxity, which are observed in later stages of RA in patients with more destructive disease, can also be seen in some patients with SLE. However, an important distinguishing features is that the joint deformities in SLE are often reducible and infrequently erosive on plain radiographs.

  Some extraarticular RA manifestations, including serositis, sicca symptoms, subcutaneous nodules, anemia, and fatigue, are other features that may also be observed in SLE. These features are more common in RA patients with more severe or advanced disease. Serologic abnormalities, such as the presence of anti-cyclic citrullinated peptides (CCP), are more supportive of the diagnosis of RA and can help distinguish the diseases. It should be recognized that the antinuclear antibodies (ANA) may be positive in up to one-half of patients with RA. Conversely, rheumatoid factor (RF) may be present in approximately one-third of SLE patients. Also, anti-CCP can be present in 5 to 10 percent of patients with SLE [74]. (See "Diagnosis and differential diagnosis of rheumatoid arthritis" and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Positive anti-CCP in other diseases'.)

- **Rhupus** – The term rhupus has been used to describe patients with overlapping features of both SLE and RA. Whether rhupus is clinically and immunologically a distinct entity, a true overlap of SLE and RA, or a subset of patients with SLE remains a matter of debate. In addition to having serologies consistent with both SLE and RA, some patients classified as rhupus may have an erosive arthropathy that is atypical for SLE. (See "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes", section on 'Early undifferentiated systemic rheumatic disease'.)

- **Mixed connective tissue disease** – Mixed connective tissue disease (MCTD) is characterized by overlapping features of SLE, systemic sclerosis (SSc), and polymyositis (PM), and by the presence of high titers of antibodies against U1 ribonucleoprotein (RNP). However, the diagnosis of MCTD is often complicated, since many of its characteristic features occur sequentially, often over a period of years. In addition, some patients with MCTD may evolve into another connective tissue disease, including SLE, during the clinical course [75]. (See "Definition and diagnosis of mixed connective tissue disease".)

- **Undifferentiated connective tissue disease** – As mentioned above, patients with undifferentiated connective tissue disease (UCTD) have signs and symptoms suggestive of a systemic autoimmune disease but do not satisfy the classification criteria for a defined connective tissue disease such as SLE or MCTD. These patients may have symptoms such as arthritis and arthralgias, Raynaud phenomenon, and serologic findings that are difficult to distinguish from early phases of SLE. The majority of patients with UCTD maintain an undefined profile and have a mild disease course [76]. (See "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes".)

- **Systemic sclerosis** – The coexistence of Raynaud phenomenon and gastroesophageal reflux is typically observed in SSc; however, these findings are nonspecific and may be seen in patients with SLE or healthy individuals. By contrast, sclerodactyly, telangiectasia, calcinosis, and malignant hypertension with acute renal failure are more consistent with SSc rather than SLE. Further, a positive ANA is present in most patients with SSc, while other serologies, such as anti-double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies that are more specific for SLE, are not commonly observed in SSc. Correspondingly, patients with SSc commonly express antibodies to an antigen called Scl-70 (topoisomerase I) or antibodies to centromere proteins. Distinguishing SSc from SLE can be particularly difficult in cases in which there is overlap of these diseases, such as in MCTD. (See "Clinical manifestations and diagnosis of systemic sclerosis (scleroderma) in adults".)

- **Sjögren's syndrome** – Patients with Sjögren's syndrome may have extraglandular manifestations that can be observed in SLE, such as neurologic and pulmonary abnormalities. However, patients with Sjögren's syndrome should have objective signs of keratoconjunctivitis sicca and xerostomia and characteristic findings on salivary gland biopsy that are not typical of SLE. Patients with Sjögren's syndrome commonly express antibodies to Ro and La antigens. Also, some patients may have SLE with associated

Sjögren's syndrome. (See "Diagnosis and classification of Sjögren's syndrome".)

- **Vasculitis** – Patients with medium- and small-vessel vasculitides, such as polyarteritis nodosa, granulomatosis with polyangiitis, or microscopic polyangiitis, may present with overlapping features of SLE, including constitutional symptoms, skin lesions, neuropathy, and renal dysfunction. However, patients with these types of vasculitides are usually ANA-negative. Rather, these patients frequently display antibodies to neutrophil cytoplasmic antigens. (See "Granulomatosis with polyangiitis and microscopic polyangiitis: Clinical manifestations and diagnosis" and "Clinical manifestations and diagnosis of polyarteritis nodosa in adults".)

- **Behçet syndrome** – Oral aphthae are present in almost all patients with Behçet syndrome and may be observed in patients with SLE. Other overlapping features include inflammatory eye disease, neurologic disease, vascular disease, and arthritis. However, the oral aphthae in Behçet syndrome are typically painful, and patients with Behçet syndrome are more commonly male and ANA-negative. Also, vascular involvement of any size (small, medium, large) is more commonly a feature of Behçet syndrome than SLE. (See "Clinical manifestations and diagnosis of Behçet syndrome".)

- **Dermatomyositis and polymyositis** – Patients with SLE can present with a low-grade myositis, whereas patients with dermatomyositis (DM) and PM generally demonstrate more overt proximal muscle weakness. A positive ANA is observed in approximately 30 percent of patients with DM and PM, compared with almost all patients in SLE. Patients with DM may have characteristic skin findings, including Gottron's papules, a heliotrope eruption, and photodistributed poikiloderma (including the shawl and V signs). Clinical findings characteristic of SLE, such as oral ulcers, arthritis, nephritis, and hematologic abnormalities, are absent in DM and PM. Patients with DM or PM may also express myositis-specific antibodies, such as anti-Jo-1. (See "Clinical manifestations of dermatomyositis and polymyositis in adults".)

- **Adult Still's disease** – Some of the clinical manifestations observed in adult Still's disease (ASD), such as fever, arthritis or arthralgias, and lymphadenopathy, are not unusual for patients with SLE. However, patients with ASD often present with a leukocytosis rather than the leukopenia observed in SLE, and they are typically negative for ANA. Markedly elevated serum ferritin concentrations are also more frequently observed in ASD. (See "Clinical manifestations and diagnosis of adult Still's disease".)

- **Kikuchi disease** – Kikuchi disease is a benign and usually self-limited form of histiocytic-necrotizing lymphadenitis. Clinical features at presentation include lymphadenopathy, fever, myalgias, arthralgias, and, less commonly, hepatosplenomegaly. Associations with SLE have been reported, but the clinical course is usually favorable, with spontaneous remission often occurring within four months. The diagnosis of Kikuchi disease is based on a lymph node biopsy, which reveals a histiocytic cellular infiltrate. (See "Kikuchi disease".)

- **Serum sickness** – Many of the clinical features observed in serum sickness, such as fever, lymphadenopathy, cutaneous eruptions, and arthralgias, are often observed in SLE. Furthermore, during severe episodes, complement measurements including C3 and C4 can be depressed, as in SLE. Unlike SLE, however, ANA are typically negative, and the course tends to be self-limited. (See "Serum sickness and serum sickness-like reactions".)

- **Fibromyalgia** – Patients with SLE may present with generalized arthralgias, myalgias, and fatigue, much like patients with fibromyalgia. However, other characteristic features of SLE, such as a photosensitive rash, arthritis, and multisystem organ involvement, are absent. However, fibromyalgia occurs more commonly in patients with systemic rheumatic diseases than in the general population. Concomitant fibromyalgia has been reported in at least 22 percent of patients with SLE [77]. (See "Clinical manifestations and diagnosis of fibromyalgia in adults".)

- **Infections** – Several viral infections can produce signs and symptoms present in SLE, including cytomegalovirus and Epstein-Barr virus. In addition, Epstein-Barr virus infection may lead to a positive ANA [78,79]. Human parvovirus B19 can cause flu-like symptoms and hematologic abnormalities such as leukopenia and thrombocytopenia, which can be observed in SLE, and patients may present with arthralgias or arthritis.

  Other viral infections that may present with multisystem involvement include HIV, hepatitis B virus, and hepatitis C virus. However, serologic assays can be diagnostic for many of these viruses. Some bacterial infections such as *Salmonella* or tuberculosis should also be considered, if appropriate.

- **Multiple sclerosis** – Although rare, patients with SLE can present with cranial neuropathies that must be distinguished from multiple sclerosis (MS). Unilateral optic neuritis and pyramidal syndrome, with lesions detected by magnetic resonance imaging (MRI) suggesting dissemination in space and time, are characteristic of MS. (See "Evaluation and diagnosis of multiple sclerosis in adults".)

- **Malignancies** – Leukemia or myelodysplastic syndromes may present with hematologic and constitutional symptoms similar to those observed in SLE. However, monoclonal expansion of B and T cells (as assessed by immunophenotyping), monocytosis, or macrocytosis can distinguish these malignancies from SLE. Patients with lymphoma also typically have additional findings such as splenomegaly, lymphadenopathy, or increased lactate dehydrogenase levels. Patients with angioimmunoblastic T cell lymphoma may be distinguished by findings on an excisional tissue biopsy, most commonly a lymph node.

- **Thrombotic thrombocytopenic purpura** – Although both patients with thrombotic thrombocytopenic purpura (TTP) and SLE may have fever and thrombocytopenia, patients with TTP also have microangiopathic hemolytic anemia, acute renal insufficiency, fluctuating neurologic manifestations, and/or low levels of ADAMSTS13. (See "Acquired TTP: Clinical manifestations and diagnosis".)

- **Other** – Some patients with psychiatric disorders (eg, bipolar disorder, substance use disorders) are thought to have SLE on the basis of a positive ANA and leukopenia that may actually be drug- or medication-induced. Thus, these patients should be evaluated for other clinical features consistent with SLE. (See "Drug-induced lupus" and "Drug-induced neutropenia and agranulocytosis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Systemic lupus erythematosus".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with

some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Lupus (The Basics)")
- Beyond the Basics topics (see "Patient education: Antinuclear antibodies (ANA) (Beyond the Basics)" and "Patient education: Systemic lupus erythematosus (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with a wide range of clinical and serologic manifestations that can affect virtually any organ. The disease course is often marked by remissions and relapses and may vary from mild to severe. (See 'Introduction' above.)
- Major clinical manifestations of SLE include the following:
  - Constitutional symptoms, such as fatigue, fever, and weight loss, are present in most patients with SLE at some point during the course of the disease. (See 'Constitutional symptoms' above.)
  - Arthritis and arthralgias occur in over 90 percent of patients with SLE and are often one of the earliest manifestations. Many patients also have skin and mucous membrane lesions. (See 'Arthritis and arthralgias' above and 'Mucocutaneous involvement' above.)
  - Cardiac disease among patients with SLE is common and can involve the pericardium, myocardium, valves, conduction system, and coronary arteries. Several vascular abnormalities, including Raynaud phenomenon, vasculitis, and thromboembolic disease, can also occur in SLE patients. (See 'Cardiac involvement and vascular manifestations' above.)
  - Renal involvement is clinically apparent in approximately 50 percent of patients and is a significant cause of morbidity and mortality. (See 'Renal involvement' above.)

- SLE-related gastrointestinal abnormalities can involve almost any organ along the gastrointestinal tract. However, the majority of symptoms are related to adverse medication reactions or infection. (See 'Gastrointestinal involvement' above.)

- Pulmonary manifestations of SLE include pleuritis (with or without effusion), pneumonitis, interstitial lung disease, pulmonary hypertension, shrinking lung syndrome, and alveolar hemorrhage. (See 'Pulmonary involvement' above.)

- Neuropsychiatric involvement of SLE consists of a broad range of neurologic and psychiatric manifestations, including cognitive dysfunction, organic brain syndromes, delirium, psychosis, seizures, headache, and/or peripheral neuropathies. (See 'Neuropsychiatric involvement' above.)

- Hematologic abnormalities can affect all three blood cell lines and include anemia, leukopenia, and thrombocytopenia. Lymphadenopathy and splenomegaly can also be observed. (See 'Hematologic abnormalities' above.)

- The initial evaluation for SLE requires a careful history and physical exam, along with selected laboratory testing to identify features that are characteristic of SLE or that suggest an alternative diagnosis. As part of the medical history and physical examination, we pay particular attention to the following symptoms and signs (see 'Evaluation' above):

  - Photosensitive skin lesions, such as a malar rash or discoid lesions
  - Painless oral or nasal ulcers
  - Hair loss that is patchy or frontal/peripheral
  - Raynaud phenomenon
  - Joint pain or swelling, which can be migratory or symmetrical
  - Symptoms of serositis/pericarditis

  We also ask about exposure to medications associated with drug-induced lupus (eg, hydralazine). (See "Drug-induced lupus".)

- We obtain a complete blood count and differential as well as serum creatinine level and urinalysis in all patients suspected of having SLE (see 'Laboratory testing' above). In addition to these routine laboratory studies, we perform selected laboratory tests that support the diagnosis of SLE if abnormal. These include antinuclear antibodies (ANA; and if positive, other specific autoantibodies, such as anti-double-stranded DNA [anti-dsDNA] and anti-Smith [anti-Sm]), antiphospholipid antibodies, C3 and C4 or CH50 complement

levels, erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels, and the urine protein-to-creatinine ratio.

- Additional studies, such as diagnostic imaging or biopsy of an involved organ, may be necessary; such testing is dictated by the clinical presentation and associated differential diagnostic possibilities. (See 'Additional testing in selected patients' above.)

- Classification criteria have been developed for SLE as a means of categorizing patients for study purposes. These criteria can be useful for clinicians in systematically documenting key disease features. (See 'Classification criteria' above.)

- The diagnosis of SLE is based upon the judgment of an experienced clinician who recognizes characteristic constellations of symptoms and signs in the setting of supportive serologic studies after excluding alternative diagnoses. Given the great variability in the expression and severity of SLE, the diagnosis of SLE is sometimes challenging, and referral to a rheumatologist with experience in this disease is often appropriate. (See 'Our diagnostic criteria' above.)

- In the absence of existing "diagnostic criteria," our general approach to the diagnosis of SLE is as follows (see 'Our diagnostic criteria' above):

    - **Definite SLE** – After excluding alternative diagnoses, we diagnose SLE in the patient who fulfills the 1997 American College of Rheumatology (ACR) criteria or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (table 3). Over time, the way in which the 2019 European League Against Rheumatism (EULAR)/ACR classification criteria potentially fit within this schema will become more clear. (See 'Definite SLE' above and 'Classification criteria' above.)

    - **Probable SLE** – There are patients who do not fulfill the classification criteria for SLE but in whom we still diagnose the disorder. These patients include those presenting with an inadequate number of ACR or SLICC criteria or those who have other SLE manifestations not included in either classification criteria. (See 'Probable SLE' above.)

      As a loose guide, we diagnose SLE in patients who have two or three of the ACR or SLICC criteria, along with at least one other feature that may be associated with but is not specific for SLE. Some of these features include the following:

        - Optic neuritis, aseptic meningitis

  - Glomerular hematuria
  - Pneumonitis, pulmonary hemorrhage, or pulmonary hypertension, interstitial lung disease
  - Myocarditis, verrucous endocarditis (Libman-Sacks endocarditis)
  - Abdominal vasculitis
  - Raynaud phenomenon
  - Elevated acute phase reactants (eg, ESR and CRP)

- **Possible SLE** – We consider SLE a possible diagnosis in individuals who have only one of the ACR/SLICC criteria, in addition to at least one or two of the uncommon features listed above. (See 'Possible SLE' above.)

- **Undifferentiated connective tissue disease** – Other patients who have even fewer features suggestive of SLE may be classified as undifferentiated connective tissue disease (UCTD). This term is used to describe patients with signs and symptoms suggestive of a systemic autoimmune disease but who do not meet the ACR criteria for SLE or another defined connective tissues disease. (See 'Undifferentiated connective tissue disease' above.)

- **ANA-negative SLE** – Less than 5 percent of patients with SLE are negative for ANA as detected by indirect immunofluorescence. The frequency of ANA-negative SLE is even lower in patients presenting at an early stage of their disease. In addition, SLE patients who have longstanding disease and/or have undergone treatment may lose ANA reactivity and become serologically negative over time.

- The differential diagnosis of SLE is broad. It includes many systemic connective diseases as well as other autoimmune disorders. (See 'Differential diagnosis' above.)

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REFERENCES

1. McKinley PS, Ouellette SC, Winkel GH. The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. A proposed model. Arthritis Rheum 1995; 38:826.

2. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology (Oxford) 2000; 39:1249.

3. Jump RL, Robinson ME, Armstrong AE, et al. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. J Rheumatol 2005; 32:1699.

4. Wang B, Gladman DD, Urowitz MB. Fatigue in lupus is not correlated with disease activity. J Rheumatol 1998; 25:892.

5. Iaboni A, Ibanez D, Gladman DD, et al. Fatigue in systemic lupus erythematosus: contributions of disordered sleep, sleepiness, and depression. J Rheumatol 2006; 33:2453.

6. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82:299.

7. Rovin BH, Tang Y, Sun J, et al. Clinical significance of fever in the systemic lupus erythematosus patient receiving steroid therapy. Kidney Int 2005; 68:747.

8. Greco CM, Rudy TE, Manzi S. Adaptation to chronic pain in systemic lupus erythematosus: applicability of the multidimensional pain inventory. Pain Med 2003; 4:39.

9. Budhram A, Chu R, Rusta-Sallehy S, et al. Anti-cyclic citrullinated peptide antibody as a marker of erosive arthritis in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Lupus 2014; 23:1156.

10. Miner JJ, Kim AH. Cardiac manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 2014; 40:51.

11. Richter JG, Sander O, Schneider M, Klein-Weigel P. Diagnostic algorithm for Raynaud's

phenomenon and vascular skin lesions in systemic lupus erythematosus. Lupus 2010; 19:1087.

12. Barile-Fabris L, Hernández-Cabrera MF, Barragan-Garfias JA. Vasculitis in systemic lupus erythematosus. Curr Rheumatol Rep 2014; 16:440.

13. Ramos-Casals M, Nardi N, Lagrutta M, et al. Vasculitis in systemic lupus erythematosus: Prevalence and clinical characteristics in 670 patients. Medicine (Baltimore) 2006; 85:95.

14. Sokalski DG, Copsey Spring TR, Roberts WN. Large artery inflammation in systemic lupus erythematosus. Lupus 2013; 22:953.

15. Dhillon PK, Adams MJ. Thrombosis in systemic lupus erythematosus: role of impaired fibrinolysis. Semin Thromb Hemost 2013; 39:434.

16. Sarabi ZS, Chang E, Bobba R, et al. Incidence rates of arterial and venous thrombosis after diagnosis of systemic lupus erythematosus. Arthritis Rheum 2005; 53:609.

17. Jung H, Bobba R, Su J, et al. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. Arthritis Rheum 2010; 62:863.

18. Danila MI, Pons-Estel GJ, Zhang J, et al. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford) 2009; 48:542.

19. Tian XP, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. World J Gastroenterol 2010; 16:2971.

20. Romero-Díaz J, García-Sosa I, Sánchez-Guerrero J. Thrombosis in systemic lupus erythematosus and other autoimmune diseases of recent onset. J Rheumatol 2009; 36:68.

21. Newman K, Owlia MB, El-Hemaidi I, Akhtari M. Management of immune cytopenias in patients with systemic lupus erythematosus - Old and new. Autoimmun Rev 2013; 12:784.

22. Silpa-archa S, Lee JJ, Foster CS. Ocular manifestations in systemic lupus erythematosus. Br J Ophthalmol 2016; 100:135.

23. Rosenbaum JT, Trune DR, Barkhuizen A, et al. Ocular, aural, and oral manifestations. In:

Dubois' Lupus Erythematosus and Related Syndromes, 8th ed, Wallace DJ, Hahn BH (Eds), Elsevier, Philadelphia 2013. p.393.

24. Gallais Sérézal I, Bouillet L, Dhôte R, et al. Hereditary angioedema and lupus: A French retrospective study and literature review. Autoimmun Rev 2015; 14:564.

25. Sawada T, Fujimori D, Yamamoto Y. Systemic lupus erythematosus and immunodeficiency. Immunol Med 2019; 42:1.

26. Abu-Shakra M, Gladman DD, Urowitz MB, Farewell V. Anticardiolipin antibodies in systemic lupus erythematosus: clinical and laboratory correlations. Am J Med 1995; 99:624.

27. Haliloglu S, Carlioglu A, Akdeniz D, et al. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. Rheumatol Int 2014; 34:1275.

28. Ehmke TA, Cherian JJ, Wu ES, et al. Treatment of osteonecrosis in systemic lupus erythematosus: a review. Curr Rheumatol Rep 2014; 16:441.

29. Zhou WJ, Yang CD. The causes and clinical significance of fever in systemic lupus erythematosus: a retrospective study of 487 hospitalised patients. Lupus 2009; 18:807.

30. Nived O, Sturfelt G, Wollheim F. Systemic lupus erythematosus and infection: a controlled and prospective study including an epidemiological group. Q J Med 1985; 55:271.

31. Hidalgo-Tenorio C, Jiménez-Alonso J, de Dios Luna J, et al. Urinary tract infections and lupus erythematosus. Ann Rheum Dis 2004; 63:431.

32. Cuchacovich R, Gedalia A. Pathophysiology and clinical spectrum of infections in systemic lupus erythematosus. Rheum Dis Clin North Am 2009; 35:75.

33. Feldman CH, Hiraki LT, Winkelmayer WC, et al. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol 2015; 67:1577.

34. Hellmann DB, Petri M, Whiting-O'Keefe Q. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. Medicine (Baltimore) 1987; 66:341.

35. Zandman-Goddard G, Shoenfeld Y. SLE and infections. Clin Rev Allergy Immunol 2003;

25:29.

36. Chen HS, Tsai WP, Leu HS, et al. Invasive fungal infection in systemic lupus erythematosus: an analysis of 15 cases and a literature review. Rheumatology (Oxford) 2007; 46:539.

37. Barber CE, Barnabe C. Another consequence of severe lupus: invasive fungal disease. J Rheumatol 2012; 39:1772.

38. Ferrari SM, Elia G, Virili C, et al. Systemic Lupus Erythematosus and Thyroid Autoimmunity. Front Endocrinol (Lausanne) 2017; 8:138.

39. Yun JS, Bae JM, Kim KJ, et al. Increased risk of thyroid diseases in patients with systemic lupus erythematosus: A nationwide population-based Study in Korea. PLoS One 2017; 12:e0179088.

40. Kuo CF, Grainge MJ, Valdes AM, et al. Familial Aggregation of Systemic Lupus Erythematosus and Coaggregation of Autoimmune Diseases in Affected Families. JAMA Intern Med 2015; 175:1518.

41. Lim SS, Drenkard C. Epidemiology of lupus: an update. Curr Opin Rheumatol 2015; 27:427.

42. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore) 1993; 72:113.

43. Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis. Medicine (Baltimore) 1971; 50:85.

44. Font J, Cervera R, Ramos-Casals M, et al. Clusters of clinical and immunologic features in systemic lupus erythematosus: analysis of 600 patients from a single center. Semin Arthritis Rheum 2004; 33:217.

45. Pons-Estel BA, Catoggio LJ, Cardiel MH, et al. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". Medicine (Baltimore) 2004; 83:1.

46. Nossent J, Kiss E, Rozman B, et al. Disease activity and damage accrual during the early

disease course in a multinational inception cohort of patients with systemic lupus erythematosus. Lupus 2010; 19:949.

47. Satoh M, Chan EK, Ho LA, et al. Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. Arthritis Rheum 2012; 64:2319.

48. Riemakasten G, Hiepe F. Autoantibodies. In: Dubois' Lupus Erythematosus and Related S yndromes, 8th ed, Wallace DJ, Hahn BH (Eds), Elsevier, Philadelphia 2013. p.282.

49. Benito-Garcia E, Schur PH, Lahita R, American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-Sm and anti-RNP antibody tests. Arthritis Rheum 2004; 51:1030.

50. Medina-Rosas J, Gladman DD, Su J, et al. Utility of untimed single urine protein/creatinine ratio as a substitute for 24-h proteinuria for assessment of proteinuria in systemic lupus erythematosus. Arthritis Res Ther 2015; 17:296.

51. Weissman BN, Rappoport AS, Sosman JL, Schur PH. Radiographic findings in the hands in patients with systemic lupus erythematosus. Radiology 1978; 126:313.

52. Ruano CA, Malheiro R, Oliveira JF, et al. Ultrasound detects subclinical joint inflammation in the hands and wrists of patients with systemic lupus erythematosus without musculoskeletal symptoms. Lupus Sci Med 2017; 4:e000184.

53. Lins CF, Lima de Sá Ribeiro D, Dourado Santos WG, et al. Ultrasound Findings on Hands and Wrists of Patients with Systemic Lupus Erythematosus: Relationship with Physical Examination. Ultrasound Med Biol 2017; 43:1764.

54. 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.

55. 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.

56. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus.

Arthritis Rheum 2012; 64:2677.

57. Pons-Estel GJ, Wojdyla D, McGwin G Jr, et al. The American College of Rheumatology and the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus in two multiethnic cohorts: a commentary. Lupus 2014; 23:3.

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

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

60. Petri M, Magder L. Classification criteria for systemic lupus erythematosus: a review. Lupus 2004; 13:829.

61. Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Arthritis Rheum 1999; 42:1785.

62. Bertsias GK, Pamfil C, Fanouriakis A, Boumpas DT. Diagnostic criteria for systemic lupus erythematosus: has the time come? Nat Rev Rheumatol 2013; 9:687.

63. Ganczarczyk L, Urowitz MB, Gladman DD. "Latent lupus". J Rheumatol 1989; 16:475.

64. Alarcón GS, Williams GV, Singer JZ, et al. Early undifferentiated connective tissue disease. I. Early clinical manifestation in a large cohort of patients with undifferentiated connective tissue diseases compared with cohorts of well established connective tissue disease. J Rheumatol 1991; 18:1332.

65. Greer JM, Panush RS. Incomplete lupus erythematosus. Arch Intern Med 1989; 149:2473.

66. Lom-Orta H, Alarcon-Segovia D, Diaz-Jouanen E. Systemic lupus erythematosus. Differences between patients who do, and who do not, fulfill classification criteria at the time of diagnosis. J Rheumatol 1980; 7:831.

67. Bodolay E, Csiki Z, Szekanecz Z, et al. Five-year follow-up of 665 Hungarian patients with undifferentiated connective tissue disease (UCTD). Clin Exp Rheumatol 2003; 21:313.

68. Ståhl Hallengren C, Nived O, Sturfelt G. Outcome of incomplete systemic lupus erythematosus after 10 years. Lupus 2004; 13:85.

69. Mosca M, Tani C, Bombardieri S. A case of undifferentiated connective tissue disease: is it a distinct clinical entity? Nat Clin Pract Rheumatol 2008; 4:328.

70. Maddison PJ, Provost TT, Reichlin M. Serological findings in patients with "ANA-negative" systemic lupus erythematosus. Medicine (Baltimore) 1981; 60:87.

71. Cross LS, Aslam A, Misbah SA. Antinuclear antibody-negative lupus as a distinct diagnostic entity--does it no longer exist? QJM 2004; 97:303.

72. Blomberg S, Ronnblom L, Wallgren AC, et al. Anti-SSA/Ro antibody determination by enzyme-linked immunosorbent assay as a supplement to standard immunofluorescence in antinuclear antibody screening. Scand J Immunol 2000; 51:612.

73. Heller CA, Schur PH. Serological and clinical remission in systemic lupus erythematosus. J Rheumatol 1985; 12:916.

74. Sauerland U, Becker H, Seidel M, et al. Clinical utility of the anti-CCP assay: experiences with 700 patients. Ann N Y Acad Sci 2005; 1050:314.

75. Cappelli S, Bellando Randone S, Martinović D, et al. "To be or not to be," ten years after: evidence for mixed connective tissue disease as a distinct entity. Semin Arthritis Rheum 2012; 41:589.

76. Mosca M, Tani C, Neri C, et al. Undifferentiated connective tissue diseases (UCTD). Autoimmun Rev 2006; 6:1.

77. Gladman DD, Urowitz MB, Gough J, MacKinnon A. Fibromyalgia is a major contributor to quality of life in lupus. J Rheumatol 1997; 24:2145.

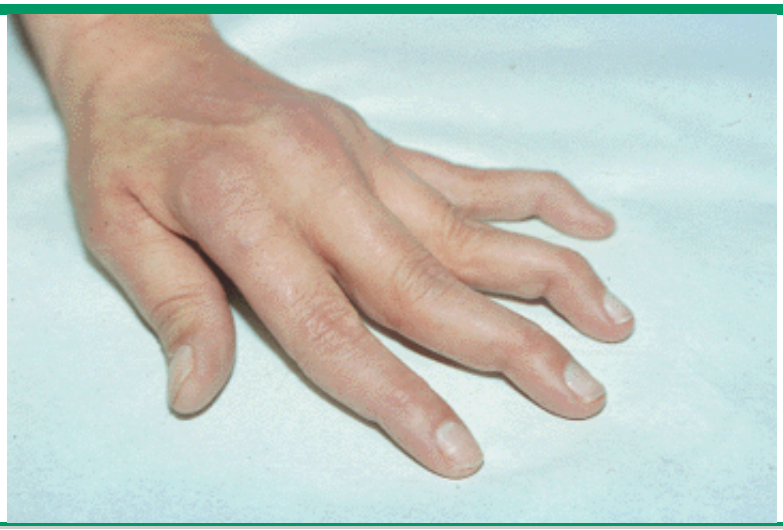
78. Sculley DG, Sculley TB, Pope JH. Reactions of sera from patients with rheumatoid arthritis, systemic lupus erythematosus and infectious mononucleosis to Epstein-Barr virus-induced polypeptides. J Gen Virol 1986; 67 (Pt 10):2253.

79. Al-Jitawi SA, Hakooz BA, Kazimi SM. False positive Monospot test in systemic lupus erythematosus. Br J Rheumatol 1987; 26:71.

Topic 4668 Version 33.0

GRAPHICS

Lupus arthritis



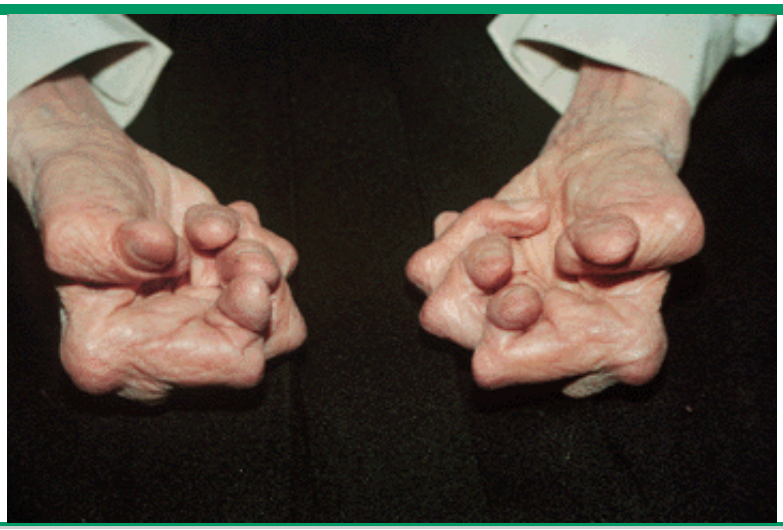
Patient with longstanding lupus has developed subluxation at the MCP joints and swan neck deformities of her fingers. These deformities are reducible (probably being due to lax tendons) and radiographs reveal no erosions or cysts, both of which differentiate these findings from those in rheumatoid arthritis.

MCP: metacarpophalangeal.

Courtesy of Peter H Schur, MD.

Graphic 78325 Version 2.0

Deforming lupus arthritis

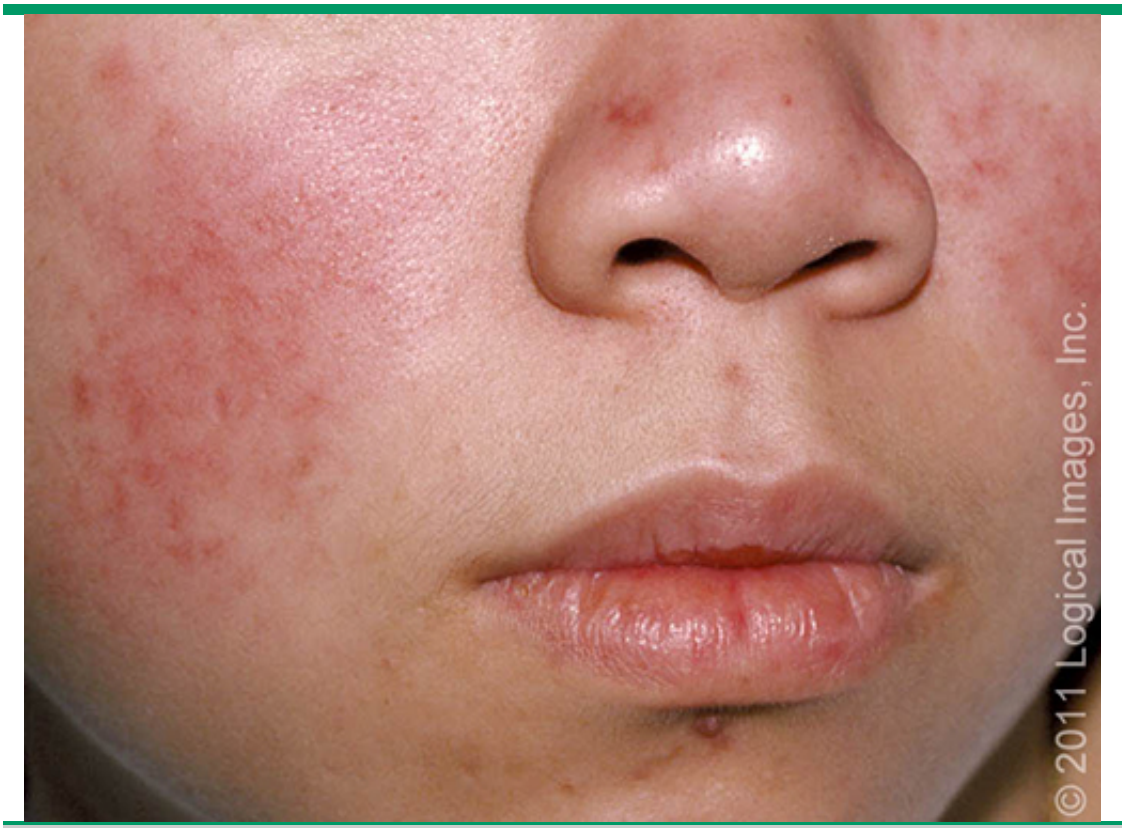


Severe hand deformities in a 75-year-old woman with lupus for more than 20 years. Such hand abnormalities are very rare.

Courtesy of Peter H Schur, MD.

Graphic 65248 Version 1.0

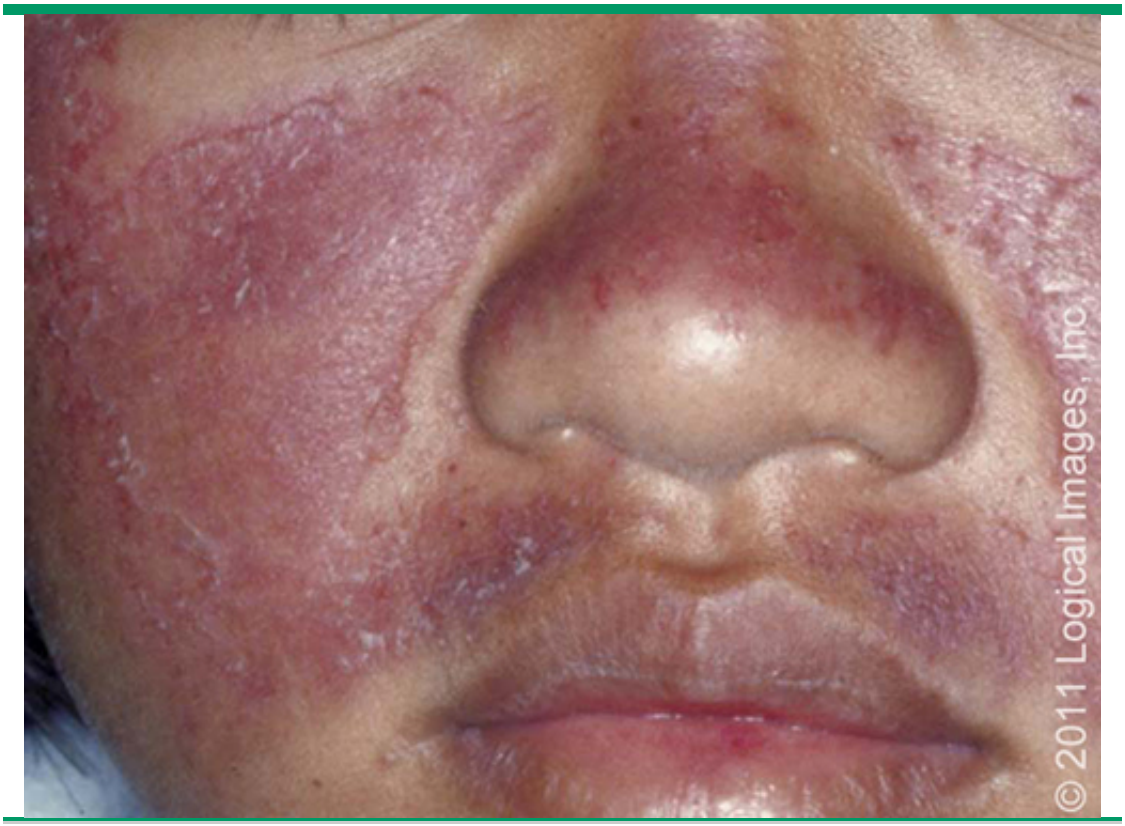
Acute cutaneous lupus erythematosus



Malar erythema and subtle edema are present in this patient with systemic lupus erythematosus.

Graphic 75781 Version 5.0

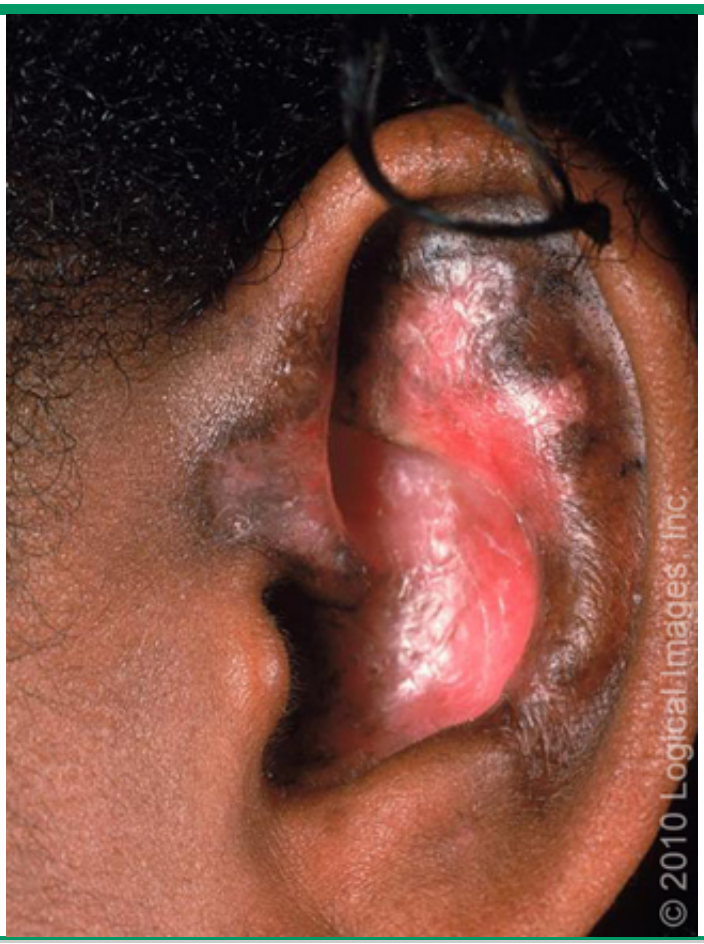
Acute cutaneous lupus erythematosus



An erythematous, edematous eruption is present on the malar area. Note the sparing of the nasolabial folds.

Graphic 55875 Version 4.0

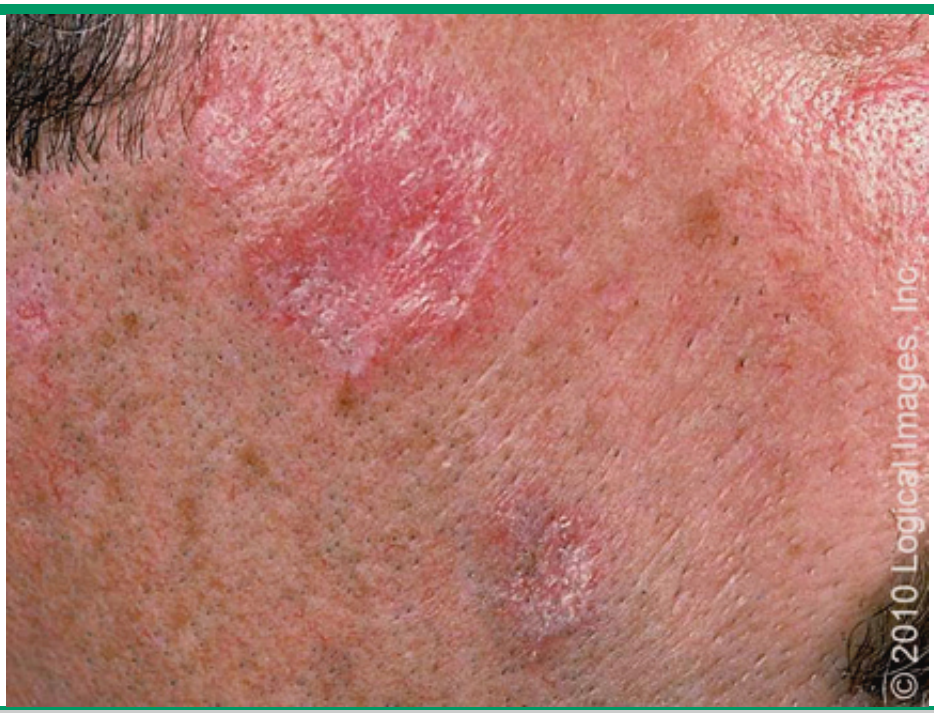
Discoid lupus erythematosus



A well-defined, erythematous plaque with scale, pigmentary alteration, and scarring is present on this patient with discoid lupus erythematosus.

Graphic 75833 Version 5.0

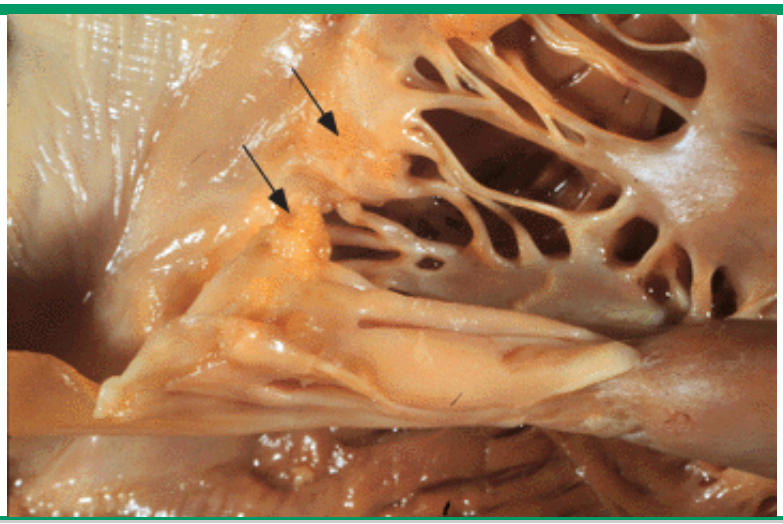
Discoid lupus erythematosus



Well-defined, erythematous plaques with scale are present on the cheek of this patient with discoid lupus erythematosus.

Graphic 64844 Version 5.0

Libman-Sacks verrucous endocarditis

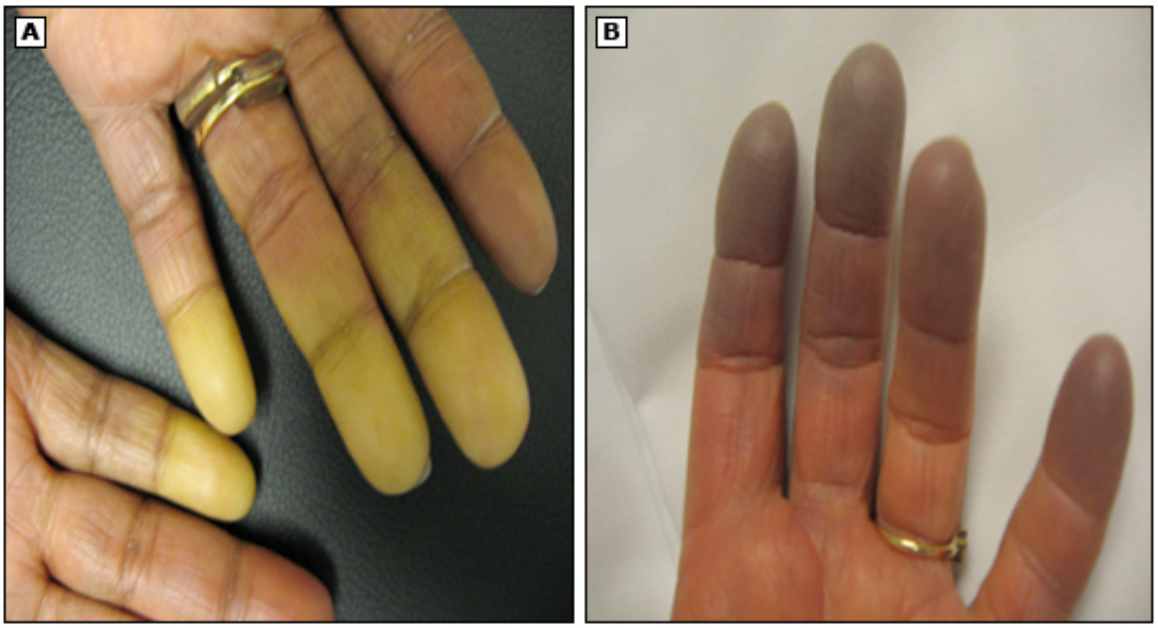


Verrucous endocarditis with valvular vegetations (arrows) in a 52-year-old woman with systemic lupus erythematosus who died of pneumonia and chronic interstitial pneumonitis. The vegetations had not been observed by echocardiography, although a cardiac murmur had been heard by auscultation. A cerebrovascular accident was also found at autopsy.

Courtesy of Peter H Schur, MD.

Graphic 79709 Version 2.0

Raynaud phenomenon



(Panel A) Sharply demarcated pallor in several fingers resulting from the closure of digital arteries.
(Panel B) Digital cyanosis of the fingertips resulting from vasoconstriction in the thermoregulatory vessel in the skin.

Courtesy of Fredrick M Wigley, MD.

Graphic 66438 Version 7.0

Frequency of signs and symptoms of systemic lupus erythematosus

Signs and symptoms	Percent at onset	Percent at any time
Fatigue	50	74 to 100
Fever	36	40 to 80+
Weight loss	21	44 to 60+
Arthritis or arthralgia	62 to 67	83 to 95
Skin	73	80 to 91
Butterfly rash	28 to 38	48 to 54
Photosensitivity	29	41 to 60
Mucous membrane lesion	10 to 21	27 to 52
Alopecia	32	18 to 71
Raynaud phenomenon	17 to 33	22 to 71
Purpura	10	15 to 34
Urticaria	1	4 to 8
Renal	16 to 38	34 to 73
Nephrosis	5	11 to 18
Gastrointestinal	18	38 to 44
Pulmonary	2 to 12	24 to 98
Pleurisy	17	30 to 45
Effusion		24
Pneumonia		29
Cardiac	15	20 to 46
Pericarditis	8	8 to 48
Murmurs		23
ECG changes		34 to 70
Lymphadenopathy	7 to 16	21 to 50
Splenomegaly	5	9 to 20
Hepatomegaly	2	7 to 25
Central nervous system	12 to 21	25 to 75
Functional		Most
Psychosis	1	5 to 52
Convulsions	0.5	2 to 20

ECG: electrocardiogram.

Adapted from: Von Feldt JM, Postgrad Med 1995; 97:79.

Graphic 70386 Version 6.0

EULAR/ACR classification criteria for SLE

Entry criterion:
- Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

If absent, do not classify as SLE

If present, apply additive criteria

Additive criteria:
- Do not count a criterion if there is a more likely explanation than SLE
- Occurrence of a criterion on at least one occasion is sufficient
- SLE classification requires at least one clinical criterion and ≥10 points
- Criteria need not occur simultaneously
- Within each domain, only the highest weighted criterion is counted toward the total score*

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		**Antiphospholipid antibodies**	
Fever	2	Anti-cardiolipin antibodies OR Anti-beta-2GP1 antibodies OR Lupus anticoagulant	2
Hematologic		**Complement proteins**	
Leukopenia	3	Low C3 OR low C4	3
Thrombocytopenia	4	Low C3 AND low C4	4
Autoimmune hemolysis	4	**SLE-specific antibodies**	
Neuropsychiatric		Anti-dsDNA antibody¶ OR Anti-Smith antibody	6
Delirium	2		
Psychosis	3		
Seizure	5		
Mucocutaneous			
Nonscarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5 g/24 hours	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		
Total score:			

Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled

Classification criteria for systemic lupus erythematosus.

EULAR: European League Against Rheumatism; ACR: American College of Rheumatology; HEp-2: human epithelial type 2; SLE: systemic lupus erythematosus; anti-beta-2GP1: anti-beta-2 glycoprotein 1; dsDNA: double-stranded DNA.

* Additional criteria items within the same domain will not be counted.

¶ NOTE: In an assay with at least 90% specificity against relevant disease controls.

From: 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(9):1400-1412. https://onlinelibrary.wiley.com/doi/full/10.1002/art.40930. Copyright © 2019 American College of Rheumatology. Reproduced with permission of John Wiley & Sons Inc. This image has been provided by or is owned by Wiley. Further permission is needed before it can be downloaded to PowerPoint, printed, shared or emailed. Please contact Wiley's permissions department either via email: permissions@wiley.com or use the RightsLink service by clicking on the 'Request Permission' link accompanying this article on Wiley Online Library (https://onlinelibrary.wiley.com/).

Graphic 122388 Version 1.0

Definitions of SLE classification criteria

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid phase ANA screening immunoassay with at least equivalent performance is highly recommended.
Fever	Temperature >38.3°C.
Leucopenia	White blood cell count $<4.0 \times 10^9$/L.
Thrombocytopenia	Platelet count $<100 \times 10^9$/L.
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH) AND positive Coombs (direct antiglobulin) test.
Delirium	Characterized by (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, (4) either (4a) acute/subacute change in cognition (eg, memory deficit or disorientation), or (4b) change in behavior, mood, or affect (eg, restlessness, reversal of sleep/wake cycle).
Psychosis	Characterized by (1) delusions and/or hallucinations without insight and (2) absence of delirium.
Seizure	Primary generalized seizure or partial/focal seizure.
Nonscarring alopecia	Nonscarring alopecia observed by a clinician.*
Oral ulcers	Oral ulcers observed by a clinician.*
Subacute cutaneous or discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician*: Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed. Discoid lupus erythematosus observed by a clinician*: Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/hematological (scalp), leading to scarring alopecia on the scalp. If skin biopsy is performed, typical changes must be present. Subacute cutaneous lupus: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Discoid lupus: interface vacuolar dermatitis consisting of a perivascular and/or periappendageal 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	Malar rash or generalized maculopapular rash observed by a clinician. If skin biopsy is performed, typical changes must be present: interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course.
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, radiograph, CT scan, MRI) of pleural or pericardial effusion, or both.
Acute pericarditis	≥2 of (1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), (2) pericardial rub, (3) electrocardiogram (EKG) with new widespread ST-elevation or PR depression, (4) new or worsened pericardial effusion on imaging (such as ultrasound, radiograph, CT scan, MRI).
Joint involvement	EITHER (1) synovitis involving 2 or more joints characterized by swelling or effusion OR (2) tenderness in 2 or more joints and at least 30 minutes of morning

	stiffness.
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24 hours urine or equivalent spot urine protein-to-creatinine ratio.
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	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 immune-fluorescence or electron microscopy, but not by light microscopy. 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 III or IV lupus nephritis on renal biopsy according to International Society of Nephrology/ Renal Pathology Society (ISN/RPS) 2003	Class III: focal lupus nephritis: active or inactive focal, segmental or global endocapillary 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 endocapillary 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.
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 A phospholipids [APL], GPL or MPL units, or >the 99th percentile) or positive anti-beta-2GP1 antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant.
Low C3 OR low C4	C3 OR C4 below the lower limit of normal.
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal.
Anti-dsDNA antibodies OR anti-Smith (Sm) antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies.

SLE: systemic lupus erythematosus; HEp-2: human epithelial type 2; CT: computed tomography; MRI: magnetic resonance imaging; GP: glycoprotein; dsDNA: double-stranded DNA.
* This may include physical examination or review of a photograph.

Graphic 122408 Version 1.0

Classification criteria for systemic lupus erythematosus

ACR criteria [1,2]		SLICC criteria [3]	
(4 of 11 criteria)*		(4 of 17 criteria, including at least 1 clinical criterion and 1 immunologic criterion; ¶ **OR** biopsy-proven lupus nephritis Δ)	
Criterion	**Definition**	**Criterion**	**Definition**
		Clinical criteria	
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds	Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); **OR** subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or clinician observation		
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions	Chronic cutaneous lupus	Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus; **OR** discoid lupus/lichen planus overlap
		Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes, such as alopecia areata, drugs, iron deficiency, and androgenic alopecia)
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a clinician	Oral or nasal ulcers	Palate, buccal, tongue, **OR** nasal ulcers (in the absence of other causes, such as vasculitis, Behçet syndrome, infection [herpesvirus], inflammatory bowel disease, reactive arthritis, and acidic foods)
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion	Joint disease	Synovitis involving 2 or more joints, characterized by swelling or effusion **OR**
			Tenderness in 2 or more joints and at least 30 minutes of morning stiffness

Serositis	Pleuritis – Convincing history of pleuritic pain or rubbing heard by a clinician or evidence of pleural effusion **OR**	Serositis	Typical pleurisy for more than 1 day, pleural effusions, or pleural rub, **OR**
	Pericarditis – Documented by ECG, rub, or evidence of pericardial effusion		Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler syndrome
Renal disorder	Persistent proteinuria greater than 500 mg/24 hours or greater than 3+ if quantitation not performed **OR**	Renal	Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, **OR**
	Cellular casts – May be red cell, hemoglobin, granular, tubular, or mixed		Red blood cell casts
Neurologic disorder	Seizures **OR** psychosis – In the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)	Neurologic	Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus); **OR** acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)
Hematologic disorder	Hemolytic anemia – With reticulocytosis **OR** Leukopenia – Less than 4000/mm^3 total on 2 or more occasions **OR** Lymphopenia – Less than 1500/mm^3 on 2 or more occasions **OR** Thrombocytopenia – Less than 100,000/mm^3 (in the absence of offending drugs)	Hemolytic anemia	Hemolytic anemia
		Leukopenia or lymphopenia	Leukopenia (<4000/mm^3 at least once) (in the absence of other known causes, such as Felty syndrome, drugs, and portal hypertension), **OR**
			Lymphopenia (<1000/mm^3 at least once) (in the absence of other known causes, such as glucocorticoids, drugs, and infection)
		Thrombocytopenia	Thrombocytopenia (<100,000/mm^3) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
		Immunologic criteria	
ANA	An abnormal titer of ANA by immunofluorescence or an	ANA	ANA level above laboratory reference range

	equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome		
Immunologic disorders	Anti-DNA – Antibody to native DNA in abnormal titer **OR** Anti-Sm – Presence of antibody to Sm nuclear antigen **OR** Positive antiphospholipid antibody on: 1. An abnormal serum level of IgG or IgM anticardiolipin antibodies **OR** 2. A positive test result for lupus anticoagulant using a standard method **OR** 3. A false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test	Anti-dsDNA	Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
		Anti-Sm	Presence of antibody to Sm nuclear antigen
		Antiphospholipid	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-beta 2-glycoprotein I (IgA, IgG, or IgM)
		Low complement	Low C3; low C4; **OR** low CH50
		Direct Coombs test	Direct Coombs test in the absence of hemolytic anemia

ACR: American College of Rheumatology; SLICC: Systemic Lupus International Collaborating Clinics; SLE: systemic lupus erythematosus; ECG: electrocardiogram; ANA: antinuclear antibodies; Anti-Sm: anti-Smith antibody; IgG: immunoglobulin G; IgM: immunoglobulin M; Anti-dsDNA: anti-double-stranded DNA; ELISA: enzyme-linked immunosorbent assay; IgA: immunoglobulin A.

* For the ACR criteria, no distinction is made between clinical and immunologic criteria in determining whether the required number has been met. The classification is based upon 11 criteria. For the purpose of identifying patients in clinical studies, a person is said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

¶ For the SLICC criteria, criteria are cumulative and need not be presently concurrently. A patient is classified as having SLE if he or she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion.

Δ Alternatively, according to the SLICC criteria, a patient is classified as having SLE if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.

References:

1. *Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271.*
2. *Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (letter). Arthritis Rheum 1997; 40:1725.*
3. *Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64:2677.*

Graphic 86633 Version 11.0

Comparison of features of musculoskeletal disease in systemic lupus erythematosus or rheumatoid arthritis

Feature	Systemic lupus erythematosus	Rheumatoid arthritis
Arthralgia	Common	Common
Arthritis	Common	Deforming
Symmetry	Yes	Yes
Joints involved	PIP>MCP>wrist>knee	PIP+MCP>wrist>knee
Synovial hypertrophy	Rare	Common
Synovial membrane abnormality	Minimal	Proliferative
Synovial fluid	Transudate	Exudate
Subcutaneous nodules	Rare	35%
Erosions	Very rare	Common
Morning stiffness	Minutes	Hours
Myalgia	Common	Common
Myositis	Rare	Uncommon
Osteoporosis	Variable	Common
Avascular necrosis	5 to 50%	Uncommon
Deforming arthritis	Uncommon	Common
Swan neck	10%, reducible	Common, not reducible
Ulnar deviation	5%, reducible	Common, not reducible

PIP: proximal interphalangeal; MCP: metacarpophalangeal.

Graphic 54324 Version 3.0

Contributor Disclosures

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