Living with Lupus

Helping Your Patient With Systemic Lupus Erythematosus

By Hussein M. Halaby, MBBS, ABIM, FRCPC; and John M. Esdaile, MD, MPH, FRCPC

In this article:

1. What is SLE?
2. How common is SLE?
3. When should SLE be suspected?
4. When should the patient be referred to a specialist?
5. What should you know about treatment?

Patient investigations:

- Hemoglobin 130 g/L
- White blood cell count 5.5 with lymphopenia, platelets 150,000 and erythrocyte sedimentation rate 60.
- Creatinine, liver function tests, and urinalysis were normal
- Serologic tests showed antinuclear antibody titre 1:640, anti-SM positive, anti-dsDNA negative, C3 and C4 reduced at 9 mg/dL

Case

Ms. S.F, 27 years old, presents to your office complaining of facial rash, fatigue, and polyarthralgia over a three-month period.

System review reveals she has had several episodes of mouth ulcers, which can be painless or painful. She denies hair loss or Raynaud's phenomenon. In the last week, she started to experience mild pleuritic chest pain, but no cough or shortness of breath. She does not smoke or drink alcohol. She has been married for two years, but never pregnant. Her family history is unremarkable for any connective tissue diseases.

On examination she looks generally well. Her blood pressure is 110/70 mmHg; her heart reate is 88 beats/minute. She has an erythematous facial skin rash, which spares the nasolabial fold. There is one ulcer on the buccal mucosa. Both wrists are mildly swollen and there is a small "bulge sign" in one knee. The rest of her examination is normal.

Lupus

What is SLE?

Systemic lupus erythematosus (SLE) is a chronic autoimmune rheumatic disease in which genetic, immunologic, hormonal, and environmental factors likely play a role in its etiology. The role of immune dysregulation is central to the pathogenesis of SLE. The increased frequency in women, particularly in childbearing years, implicates increased estrogenic activity. Environmental factors include triggers, such as ultraviolet light and certain drugs (*i.e.,* hydralazine, procainamide, minocycline, methyldopa, and chlorpromazine).

How common is SLE?

SLE tends to affect more females compared to males. In adults, the ratio ranges from 10 to 15 women to one man.[1] The incidence of SLE diagnosis has tripled over the last four decades. Currently, the adjusted annual incidence of SLE is 5.6 per 100,000. The age- and sex-adjusted prevalence rate is approximately 1.2 per 1,000.[2]

When to suspect SLE?

Because of its variability in clinical presentation, SLE has been called the "Great Masquerader." While the American College of Rheumatology has developed 11 classification criteria, there is no reason to attempt to remember them.[3] The key to recognising SLE is to be aware that, while the presentation is variable, it is a multisystem disease. Two out of the seven body systems are typically involved (Table 1). Another tip-off for considering a connective tissue disease, such as SLE, is the presence of otherwise unexplained constitutional features, such as fever or fatigue.

Practice Pointer

When to refer a patient to a rheumatologist?

The American College of Rheumatology recommendations for referral to a rheumatologist were published in 1999 and include the following:

- To confirm the diagnosis.
- To assess disease activity and severity.
- To advise on general disease management.
- To manage uncontrolled disease.
- To manage organ involvement or life-threatening disease.
- To manage/prevent treatment toxicity.
- In other specific circumstances, including the antiphospholipid syndrome, pregnancy, surgery.

Dr. Halaby is clinical fellow, division of rheumatology, department of medicine, University of British Columbia, Vancouver, British Columbia.

Dr. Esdaile is professor and head, division of rheumatology, department of medicine, University of British Columbia, Vancouver, British Columbia.

In the setting of a multisystem disease, SLE can be excluded by a negative antinuclear antibody (ANA) test. A positive ANA test does not make the diagnosis, as up to 5% of the normal population may be positive. Also, a positive ANA is even more common in other inflammatory and autoimmune conditions.

In the setting of the involvement of two or more systems (Table 1), a positive ANA calls for more specific autoantibody testing—anti-double-stranded DNA, anti-Sm, anti-La (SSA), anti-Ro (SSB), anti-RNP, and anti-cardiolipin antibodies (Table 2). SLE involves not only multiple systems, but also multiple autoantibodies. The low platelet count, low white blood cell count, low lymphocyte count, hemolytic anemia, and biologic false positive venereal disease research laboratory (VDRL) slide test, that can occur in SLE, all arise from autoantibodies.

As useful as the determination of autoantibodies is in diagnosis, these tests cannot be relied upon to guide treatment. The well-proven adage "Treat the patient, not the serology" is definitely applicable here.

How should I follow my SLE patient?

Given the rarity of SLE in any single practice, patient management should be carried out in conjunction with a rheumatologist or other suitable specialist. Lifelong monitoring is required for most patients with SLE. At least quarterly, a history and physical examination focusing on SLE manifestations (Table 1) should be performed.

At each quarterly followup visit, the following investigations should be obtained: com-

Table 1
Checking for the involvement of more than one system

System	Manifestations	Frequency at onset
Skin/mucocutaneous	Photosensitivity	29%
	Butterfly rash	40%
	Discoid lesions	6%
	Oral ulcers	11%
	Raynaud's phenomenon	18%
	Alopecia	–
Musculoskeletal	Arthritis	69%
Serositis	Pleuritis, Pericarditis, Peritonitis	17%
Nephropathy	Proteinuria, Cellular cast, High creatinine	16%
Neurologic	Seizure, Psychosis	12%
Hematologic	Thrombocytopenia	9%
	Hemolytic anemia	4%
	Leukopenia	—
	Lymphopenia	—
	Lymphadenopathy	7%
Pulmonary	Acute lupus pneumonitis	3%

Adapted from: Cervera R, Khamashta MA, Font J, et al: Systemic lupus erythematosus clinical and immunologic patterns of diseases expression in a cohort of 1,000 patients. Medicine (Baltimore) 1993; 72(2):113-24.

Table 2
Tests for diagnosing SLE

Investigation	Frequency	Clinical importance
ANA	> 98%	Best available test to exclude SLE.
Anti-dsDNA	60%-70%	Very specific for SLE.
Anti-Sm	25%-30%	Less common than anti-dsDNA, but also very specific for SLE.
Anti-Ro, Anti-La	15%-30%	Dry eyes and mouth, cutaneous lupus, photosensitivity. Maternal antibodies associated with increased risk of neonatal lupus.
C3, C4	Variable	Low levels common in lupus.
Anti-RNP	30%-40%	More associated with Raynaud's phenomenon and arthritis.
Antiphospholipid	30%	Arterial and venous thrombosis. antibodies

plete blood count, creatinine and urinalysis.[4] Many rheumatologists advise checking the C3, C4 level and anti-dsDNA level quarterly.[5,6]

What about treatment?

SLE is a lifelong disease. The better informed a patient is, the better their outcome will be. Education about the disease can be supplemented from local or international organisations, such as Lupus Canada, The Arthritis Society of Canada, and the Arthritis Society Help Line (1 800 321-1433).

Treatment of SLE is evolving rapidly, so collaboration with a specialist knowledgeable in SLE is key. Choose a consultant who is very familiar with SLE. Often, this will be a rheumatologist. Frequently, other specialists are required. The primary-care physician must provide all the usual preventive care and treatment and may often help with disease monitoring. Myocardial infarction and stroke are increased more than 10-fold, and are now

major causes of both morbidity and mortality in SLE. As such, all lupus patients should be evaluated for cardiovascular risk factors (*i.e.,* smoking, hypertension, diabetes, elevated cholesterol, elevated homocysteine).[7] These risk factors should be modified and treated aggressively. The role of the primary-care physician in assessing risk factors and intervening to reduce risks, such as smoking, hypertension, and hyperlipidemia cannot be over stressed.

All those with lupus should avoid sun exposure. Sunscreen with SPF against UVA and with a UVB of at least 30 should be applied 30 minutes before exposure.

Non-pharmacologic treatment

Adequate rest and sensible diet are advisable for all. A multivitamin with vitamin D is reasonable, given the advice below to avoid the sun. Regular exercise, except during severe flares, maintains muscle tone and bone strength, decreases cholesterol and blood pressure, and reduces fatigue.

People with lupus should avoid sun exposure. Sunscreen with skin protection factor against ultraviolet A, with an ultraviolet B of at least 30 should be applied 30 minutes before exposure. Wide-brimmed hats, long-sleeved blouses/dresses/shirts, and trousers are advisable. Everyone with lupus, but especially those on immunosuppressive medications, should receive influenza and pneumococcal vaccinations.

Lupus

Pharmacologic treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs)

These drugs help control mild inflammation. These drugs also benefit fever, myalgia, arthralgia and arthritis, and mild serositis. Use of NSAIDs should be avoided in patients with lupus nephritis. NSAID hepatitis and NSAID induced aseptic meningitis are common in SLE. Blood pressure and renal function must be monitored particularly carefully in patients taking NSAIDs.

Everyone with lupus, but especially those on immunosuppressive medications, should receive influenza and pneumococcal vaccinations.

Antimalarial drug (hydroxychloroquine)

This drug is widely used in treating SLE. Hydroxychloroquine has a long half-life, and is therefore slow-acting. It benefits most skin lesions in SLE, as well as arthritis, serositis, and fatigue. Also, hydroxychloroquine may lower serum cholesterol, and reduce venous thrombosis.[8] Discontinuing hydroxychloroquine is frequently associated with disease flare-up.[9]

The maximum dose of hydroxychloroquine is 400 mg/day. The dose should not exceed 6.5 mg/kg/day to minimise the risk of retinal toxicity. Although treatment need not be withheld pending an ophthalmologic examination, one should be performed within six months of starting hydroxychloroquine, and every 12 to 18 months thereafter. Most patients with SLE benefit from taking hydroxychloroquine.

Topical corticosteroids

When applied directly on skin lesions, topical corticosteroids are effective in SLE. Ointments are generally used for dry skin and creams for oily skin. Fluorinated forms are stronger than non-fluorinated and are more likely to cause side effects, such as thinning of the skin. Generally the agents are applied one to four times daily.

Systemic corticosteroids, like oral prednisone, are used frequently in SLE patients. Low-dose therapy (0.25 mg/kg/day) is used for mild manifestations, including arthritis, mild serositis, and skin rashes, that are unresponsive to other remedies, such as NSAIDs and hydroxychloroquine. Moderate doses (0.5 mg/kg/day) are effective for high fever, pleuritis, pericarditis, and mild nephritis. Higher doses (1 mg/kg/day) are reserved for more severe manifestations.

Because systemic corticosteroids increase the risk of osteoporosis, patients should receive sufficient calcium (1.0 g/day to 1.5 g/day) and vitamin D (800 IU/day). If the prednisone dose is 7.5 mg/day or greater for more than three months, a bisphosphonate must be added to prevent osteoporosis. Other tests for monitoring corticosteroid side effects include a serum glucose every three to six months, total cholesterol yearly, and bone densitometry yearly.[4]

Because corticosteroids are believed to increase the frequency of myocardial infarction and stroke, the objective of treatment is to always minimise corticosteroid use.

Immunosuppressives

Immunosuppressives, such as azathioprine, and cyclophosphamide, mycophenolate mofetil, and

Take-home message

- SLE is a disease with a highly variable presentation, course, and prognosis. While SLE will likely be rare in a given primary-care practice, keep the diagnosis in the back of the mind when confronted by a multisystem disease.
- A negative ANA test makes the diagnosis unlikely. When SLE is diagnosed, the primary care physician has a key role to play in regular followup to monitor cardiovascular risk factors, encourage compliance, and provide support and counselling.
- The good news is that treatment and outcomes are improving. Early aggressive treatment is the watchword.

cyclosporine, are commonly used. These drugs are reserved for more severe disease or to spare the use of corticosteroids. In severe lupus nephritis, intravenous cyclophosphamide is more effective than intravenous methylprednisolone.[10] Following cyclophosphamide use, yearly urine cytology and Papanicolaou tests are recommended for life.[5]

Other therapies

There are many new experimental therapies under active investigation. These include lefluno-mide, tacrolimus, and biologics (anti-CD 40, antiC5a, rituximab, LJP 394, and anti-IL10). CME

References

1. Lahita, RG: The role of sex hormones in systemic lupus erythematosus. Cur Opin Rheumatol 1999; 11(5):352-6.
2. Thumboo J, Uramoto K, O'Fallon WM, et al: A comparative study of the clinical manifestations of systemic lupus erythematosus in Caucasians in Rochester, Minnesota, and Chinese in Singapore, from 1980 to 1992. Arthritis Rheum 2001; 45(6):494-500.
3. Tan EM, Cohen AS, Fries JF, et al: The 1982 revised criteria for classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25(11):1271-7.
4. Gladman DD, Urowitz MB, Esdaile JM, et al: Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum 1999; 42(9):1785-96.
5. Ho A, Barr SG, Magder LS, et al: A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. Arthritis Rheum 2001; 44(10):2350-7.
6. Ho A, Magder LS, Barr SG, et al: Decreases in anti-double-stranded DNA levels are associated with concurrent flares in patients with systemic lupus erythematosus. Arthritis Rheum 2001;44(10):2342-9.
7. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: Comparison with the Framingham study. Am J Epidemiol 1997; 145(5):408-15.
8. Petri M, Lakatta C, Magder L, et al: Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: A longitudinal data analysis. Am J Med 1994; 96(3):254-9.
9. The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. N Engl J Med 1991; 324(3):150-4.
10. Boumpas DT, Austin HA, Vaughn EM, et al: Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992; 340(8822):741-5.

Systemic Lupus Erythematosus

As presented at the University of British Columbia
13th Annual Topics in Internal Medicine for Primary Care Physicians
By Hussein Halaby, MBBS, ABIM, FRCPC; and John Esdaile, MD, MPH, FRCPC

1. What is systemic lupus erythematosus (SLE)?

SLE is a chronic autoimmune rheumatic disease in which genetic, immunologic, hormonal, and environmental factors likely play a role in its etiology. The role of immune dysregulation is central to the pathogenesis of SLE.

2. How common is SLE?

SLE tends to affect more females compared to males. In adults, the ratio ranges from 10 to 15 women to one man. The incidence of SLE diagnosis has tripled over the last four decades.

3. When to suspect SLE?

Because of its variability in clinical presentation, SLE has been called the "Great Masquerader." In order to recognise SLE, the physician should remain aware that, while the presentation is variable, it is a multisystem disease. Two out of the seven body systems are typically involved. Another tip-off for considering a connective tissue disease, such as SLE, is the presence of otherwise unexplained constitutional features, such as fever or fatigue.

4. When is a referral to a rheumatologist needed?

- To confirm the diagnosis.
- To assess disease activity and severity.
- To advise on general disease management.
- To manage uncontrolled disease.
- To manage organ involvement or life-threatening disease.
- To manage/prevent treatment toxicity.
- In other specific circumstances, including antiphospholipid syndrome, pregnancy, surgery.

5. As a GP, how should I follow my SLE patient?

Given the rarity of SLE, patient management should be carried out in conjunction with a rheumatologist or other suitable specialist. Lifelong monitoring is required for most patients with SLE. At least quarterly, a history and physical examination focusing on SLE manifestations should be performed.

For an in-depth article on SLE, please go to page 88.