

A middle aged woman with fever and a rash

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SELF-ASSESSMENT QUIZ

A 34-year-old woman presented to the emergency clinic, complaining of fatigue and mild arthralgias and myalgias. The fatigue and arthralgias have been present for at least the previous three months, during which time she had occasional fever as high as 38.5° C that had occurred in the absence of respiratory, gastrointestinal, or urinary symptoms. She did not give any history of drug intake prior to the onset of symptoms. She also had an erythematous rash involving her cheeks on exposure to sun, and occasionally a rash on her hands.



Figure 1. Erythematous, elevated, pruritic, lesion across the face in a malar distribution

Initial physical examination revealed erythema on her face (Fig. 1). Multiple well defined superficial ulcers with surrounding erythema were observed on the hard palate on oral mucosal examination (Fig 2). Joint examination showed mild bilateral wrist tenderness but no swollen joints. On laboratory examination the patient was positive for rheumatoid factor and anti nuclear antibody (ANA). Her serum creatinine level was 1.2 mg/

dl (1.0-1.5). Urinalysis showed proteinuria but no red blood cells or red blood cell casts.

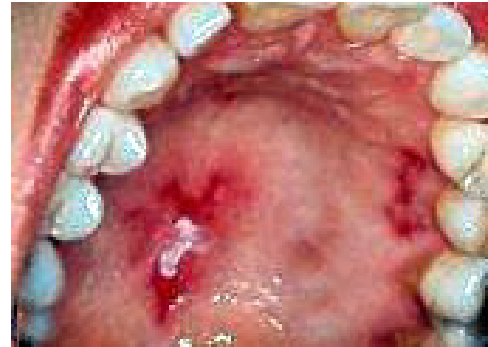


Figure 2. Superficial ulcers on the hard palate with surrounding erythema

Questions

1. What is the diagnosis of this condition?
2. What are the other causes of positive ANA?
3. How could the physician monitor the disease activity?
4. In a pregnant patient having this disease, what are the effects on the fetal outcome?
5. What is the prognosis of this disorder?

(Please turn to next page for answers.)

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Answers

1. What is the diagnosis of this condition?

Systemic lupus erythematosus (SLE).

SLE was first described in 1828. Its name includes *lupus*, from the Latin term for wolf, because the disease often produces a rash that extends across the bridge of the nose and upper cheekbones and was thought to resemble a wolf bite. The term *erythematosus* (from the Greek word for red) refers to the color of the rash, and the term *systemic* is used because the disease can affect organs and tissues throughout the body. The condition is more common in women than in men (ratio 9:1).¹

2. What are the other causes of positive ANA?

In the absence of systemic lupus erythematosus, the most common cause for a positive ANA test is the presence of another connective tissue disease. Diseases that are often associated with a positive ANA test include Sjögren's syndrome (68% of affected patients), scleroderma (40% to 75%), rheumatoid arthritis (25% to 50%), and juvenile rheumatoid arthritis (16%). An ANA test also can be positive in patients with fibromyalgia. In patients with diseases other than systemic lupus erythematosus, ANA titers usually are lower, and the immunofluorescent pattern is different.² Age over 60 years in healthy individuals and female sex are associated with a higher frequency of positive ANA tests.³ Regions in which malaria is endemic have high frequencies of positive ANA tests.⁴

3. How could the physician monitor the disease activity?

The activity of the disease varies over time for most SLE patients. When monitoring SLE patients, it is essential to quantify such variations, and for this reason several scoring systems have been constructed to assess disease activity. One scoring system used frequently in clinical studies is the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, which is calculated by summing the weights of 24 different signs and symptoms.

Severe manifestations of the disease that can be life threatening, such as the involvement of the central nervous system and vascular manifestations are given high

weights. The descriptors are seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident or vasculitis (weight 8 each), arthritis, myositis, urinary casts, hematuria, proteinuria or pyuria, (weight 4 each), rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement or increased DNA binding (weight 2 each), fever, thrombocytopenia or leukopenia (weight 1 each).⁵

Zecevic et al.⁶ have explored establishing a correlation between LE-specific and LE-non-specific cutaneous lesions and disease activity measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Patients with LE-non-specific skin manifestations had significantly increased disease activity compared to those with only LE-specific lesions. The number of different skin lesion types also correlated with disease activity. It was significantly increased in a group with three different types of lesion, either specific or non-specific. Patients with only one type of lesion had mild disease. An intermediate disease activity was found in the group with two different lesion types. Lupus-specific skin manifestations serve primarily as an important diagnostic clue. In conclusion, patients with LE-non-specific lesions have significantly more active SLE than those with LE-specific lesions and may therefore require more intensive therapy and disease monitoring.

4. In a pregnant patient having this disease, what are the effects on the fetal outcome?

Only about one half of pregnant patients with systemic lupus erythematosus deliver a full-term baby of normal weight.⁷ Causes of abnormal pregnancies are about equally divided among fetal death, prematurity, and intra-uterine growth retardation. Maternal hypertension or renal disease, previous history of fetal death, or the presence of antiphospholipid antibody increases the risk. In pregnant women, antiphospholipid antibody is associated with fetal death (primarily in the second trimester).⁸ Surprisingly, lupus activity itself does not independently affect pregnancy outcome. Children born alive to mothers with systemic lupus erythematosus are generally as healthy as other newborns of similar weight and gestational age. As they grow, some may suffer mild but specific verbal processing

defects that do not affect overall intelligence.⁹ Neonatal lupus is a rare syndrome that occurs in a minority of infants delivered only by mothers who have antibodies to the Ro/SS-A or La/SS-B antigens, or both. Approximately one third of patients with systemic lupus erythematosus have one or both of these antibodies. Cutaneous neonatal lupus develops in fewer than 25% of infants born to mothers with systemic lupus erythematosus who have the associated antibodies; congenital heart block occurs in fewer than 3%.¹⁰ The occurrence and severity of neonatal lupus are unrelated to maternal disease activity or severity. When a viable infant with deteriorating heart function is observed, early delivery is indicated. Some apparently well women who have delivered a child with neonatal lupus later develop systemic lupus erythematosus.^{11,12}

5. What is the prognosis of this disorder?

Survival rates in patients with SLE have increased from 50% at five years in the 1950s to 80-90% at 10 years in the 1990s. The explanations for this improvement include early diagnosis, recognition of mild disease, advances in medical therapy, and improved supportive care, including renal replacement therapy.¹³ Morbidity and mortality rates in this disease are bimodal, with early events related to disease activity or infection and later events often due to premature vascular disease such as stroke and myocardial ischemia.¹³ More than 90% of patients with SLE die from one of five causes: complication of kidney disease, infections, central nervous system lupus, blood clots, or cardiovascular complications. Deaths from lupus tend to occur either early in the course of the disease among those who have active aggressive lupus and do not respond well to treatment, or after 15 to 20 years from continuously active inflammation or complications of therapy.¹⁴

Discussion

SLE, is a chronic autoimmune disease with tissue damage caused by autoantibodies and immune complexes. The disease has a wide spectrum of clinical manifestations that include non-erosive arthritis and skin lesions, but also inflammation in internal organs that cause nephritis, pleuritis, pericarditis and nervous system involvement. General symp-

toms such as malaise, fever and fatigue are also common in SLE patients. Most patients have antinuclear antibodies (ANA), and during active disease leukopenia and/or complement consumption are frequently seen. The disease is also varyingly active, with periods of exacerbations that are followed by remissions.¹⁵

The cause of systemic lupus erythematosus has not been established. Predisposing factors include genetic factors (certain types of human leukocyte antigens and null complement alleles), environmental factors including sun exposure, some drugs such as sulfa antibacterials, and hormonal factors.¹⁵

More than 70 medications have been implicated as possible etiologic agents in SLE.¹⁶ Included in this list are several antihypertensive medications, of which hydralazine is the best described and which poses the most significant risk. Captopril and enalapril have been the only two angiotensin-converting enzyme inhibitors shown to induce lupus-like diseases.¹⁶

Induction of ANAs by certain medications is common. In more than half the patients taking procainamide and slightly less than half taking hydralazine, ANAs will develop. However, a lupus-like disease occurs in only a small fraction of these patients.¹⁷ Therefore, the presence of ANAs in no way implies disease. It has also been described that some patients with drug-induced lupus (DIL) caused by quinidine or minocycline have serum that is ANA-negative.¹⁸ Etanercept is a new drug for the treatment of rheumatoid arthritis that has recently been implicated as a cause of drug-induced SLE.¹⁹ Reports of positive ANAs and drug-induced SLE have been associated with infliximab.²⁰ Simvastatin has been linked to some isolated cases of a drug-induced SLE-like syndrome.²¹ Drug-induced lupus can be differentiated from the idiopathic disease on genetic and immunologic grounds. Furthermore, it is mild and reversible on stopping the drug, renal disease and double stranded anti-DNA are rare (although antibodies specific for histones may be present) and the sex ratio is equal.

It is proposed that both genetic susceptibility and environmental triggers influence the development of the above abnormal characteristics in SLE. The environmental factors work together with the

susceptibility genes (present in certain individuals) initiating the activation of T- and B-lymphocytes, and resulting in the production of autoantibodies and immune complexes. SLE patients are also more susceptible to damage from autoantibodies and immune complexes because they can make more of these harmful subsets and/or they cannot properly regulate hyperactivated B- and helper T-cells and their products due to impaired down-regulating mechanisms. This may result in tissue damage attributable to prolonged exposure to autoantibodies and immune complexes. The genetic susceptibility of individuals with SLE is due to the inheritance of genes that allow immune over-response, and/or regulatory under-response, or large quantities of target antigens in particular tissues. All that is required is a very slight increase or decrease in the expression of the genes that influence the above factors to allow SLE to develop after an environmental stimulus provokes an autoimmune response. In a very few individuals a single gene may be responsible. However, in 95% of SLE cases multiple genes are involved. Environmental factors may trigger a flare in patients already diagnosed with SLE.

The diagnosis of systemic lupus erythematosus requires a thorough history, a physical examination and laboratory tests, including a complete blood cell count, chemistry panel and urinalysis. The American College of Rheumatology (ACR) has developed criteria to classify patients with a diagnosis of systemic lupus erythematosus for research studies. These classification criteria are often helpful clinically, especially since they emphasize the multisystemic nature of the disease.²² If a patient displays four or more of the following symptoms (either serially or simultaneously), the patient may be diagnosed as having SLE:

- (a) a red rash over cheeks and the bridge of the nose (malar rash);
- (b) a red, scaly rash on the face, scalp, ears, arms or chest (discoid rash);
- (c) an unusual reaction to the sun (photosensitivity);
- (d) small sores on the moist lining of the mouth (oral ulcers) or nose;
- (e) arthritis characterized by tenderness, swelling or fluid in two or more peripheral joints;
- (f) documented pleuritis or pericarditis;

- (g) excessive protein and/or cellular casts in the urine;
- (h) seizures and/or psychosis (not accounted for by drug reactions or identified metabolic disorders);
- (i) a decrease in the number of red and white blood cells or platelets;
- (j) immunologic disorder (blood test indicates positive LE cell preparation, anti-DNA, positive anti-Sm or false positive syphilis test);
- (k) positive ANA blood test.

In 1997, an update of these criteria was published, where two changes were proposed; deletion of positive LE cell preparation, and addition of positive antiphospholipid antibodies.²³

The most important cutaneous presentation of SLE is the classic malar 'butterfly' rash; it usually presents abruptly after exposure to sunlight and lasts for several days or weeks. The butterfly rash presents as an erythematous, elevated, pruritic, and sometimes painful lesion across the face in a malar distribution that on biopsy shows nonspecific inflammation, although immune deposits at the dermal-epidermal junction are seen by immunofluorescence. Approximately two thirds of patients with SLE have photosensitivity, defined as a skin rash due to an unusual reaction to sunlight. Solar radiation may also exacerbate systemic disease activity. Reports indicate that up to 70% of patients with photosensitivity are positive for antiSSA (AntiRo) antibodies.²⁴ Ulceration of the mouth or, less commonly, the nose or vagina may or may not be painful, but it is also usually self limiting. Raynaud's phenomenon occurs in about half of patients at presentation, but it is less common and usually milder than with scleroderma or related syndromes. Conversely, most patients who present to their general practitioner with Raynaud's syndrome will not have systemic lupus erythematosus.

Generalized arthralgia, with pronounced morning stiffness, but little to find on examination is characteristic, and pain may be considerable. Although symptoms may mimic early rheumatoid arthritis, joint swelling (synovitis) is much less noticeable. Severe fatigue in conjunction with some of the above symptoms may reflect a flare up of the disease. Chronic fatigue, however, is almost invariable

in established systemic lupus erythematosus and may reflect underlying depression or cardiovascular deconditioning.²⁵

Renal disease occurs in 20-50% of all patients at some time during their disease, but end stage renal failure is rare (<5%). Clinically active renal disease is manifested by the presence of proteinuria, cellular casts, hematuria, or pyuria in the absence of other causes of kidney damage. The start of disease may be insidious, and patients should therefore have regular dipstick testing of their urine for protein to facilitate early and aggressive treatment.²⁵

Neuropsychiatric involvement of patients with SLE ranges from simple headache to CNS vasculitis. Other unusual manifestations of CNS lupus include Parkinsonism, cerebellar ataxia, pseudotumor or cerebrae, hypothalamic dysfunction, aseptic meningitis (related to NSAID use), myasthenia-like syndrome, Eaton-Lambert syndrome, and thrombotic thrombocytopenic purpura. Peripheral nervous system involvement of SLE is also noted in approximately 10% of patients and includes sensory or motor myopathies, Guillain Barré-like syndrome, and mononeuritis multiplex.²⁶ 'Lupus headache' is extremely uncommon and is usually associated with other features of active disease; it may be unremitting and unresponsive to simple analgesics. Migraine is more common in patients with lupus than in the general population, particularly in patients with antiphospholipid antibodies.²⁵

Anemia, leukopenia, and thrombocytopenia are frequent manifestations of SLE. Patients with SLE often have normocytic normochromic anemia. Leukopenia with white blood cell counts of less than 4000/mm³ or lymphopenia with cell counts less than 1500/mm³ on two or more occasions is part of the diagnostic criteria of SLE. Thrombocytopenia with a platelet count of less than 100,000/mm³ in the absence of other causes is found in up to 25% of SLE patients. Thrombocytopenia is often a marker of severe disease with poor prognosis.²⁷ It is important to recognize that a positive antinuclear antibody (ANA) test is also reported in up to 30% of patients with chronic idiopathic thrombocytopenic purpura.²⁸ SLE may affect the cardiopulmonary system. Pleurisy and pericarditis may be presenting features, and pleuritic pain may mimic the pain of infection or embolism.²⁵

One of the major complications of systemic lupus erythematosus is premature or accelerated atherosclerosis. Studies conducted worldwide have suggested that somewhere between 6 and 10 per cent of patients with systemic lupus erythematosus have clinically recognized premature atherosclerosis.²⁹ Patients with systemic lupus erythematosus have higher levels of homocysteine, a known risk factor for atherosclerosis.³⁰

Gastrointestinal symptoms in patients with SLE are relatively common and present as abdominal pain, anorexia, nausea, and/or vomiting. Peritoneal inflammation is the most likely cause of GI symptoms, but mesenteric vasculitis or pancreatitis are dangerous complications of SLE and need to be considered in the presence of abdominal symptoms.³¹

Currently, minor manifestations of systemic lupus erythematosus (cutaneous, musculoskeletal, fatigue) are managed with non-steroidal anti-inflammatory drugs (NSAIDs), antimalarial drugs (particularly hydroxychloroquine) and low-dose corticosteroids. Hydroxychloroquine causes a reduction in flares and a lower risk of organ-threatening dissemination.³² An ability to lower blood glucose and cholesterol levels, combined with an antiplatelet effect, makes this drug an attractive therapeutic option for all patients with lupus. The risk of retinal toxicity with hydroxychloroquine may have been overstated in the past, and the Royal College of Ophthalmologists, London recommends routine ophthalmic screening in adults only if the dosage of hydroxychloroquine is greater than 6.5 mg/kg lean body weight per day, if there is impaired renal or hepatic function, if visual symptoms develop, or if the duration of therapy extends beyond five years.³³ Treatment-resistant cutaneous lupus has been treated with thalidomide, with improvement in up to 84% of patients.³⁴ However, its use will remain limited because of the risk of fetal abnormalities and the high rate of neuropathy. There is increasing concern about the long term use of steroids, including low-dose therapy, in patients with lupus. With time, musculoskeletal damage, including avascular necrosis and osteoporosis, heads the organ damage list. If the prednisolone dose is increased by 10 mg, the average weight gain is 2 kg, and increases in serum cholesterol level and mean arterial blood pressure occur.³⁵

The management of major organ involvement (e.g. renal or neuropsychiatric) necessitates combining steroids and immunosuppressants such as cyclophosphamide and azathioprine, and, more recently, cyclosporin A and myco-phenolate mofetil. Although successful in the management of lupus nephritis, high-dose pulse cyclophosphamide (0.75-1.0 g/m² monthly) and steroids have been associated with significant toxicity, including premature ovarian failure in 55% and infection in 29% of patients.³⁶ A short, low-dose cyclophosphamide regimen followed by azathioprine has been found to be a successful combination, with reduced incidence of ovarian failure and infection.³⁷

Mycophenolate mofetil has been found to be effective, including in some patients who have shown resistance to cyclophosphamide.³⁸ Cyclosporin has been shown to reduce proteinuria in patients with membranous and diffuse proliferative nephropathy. However, concern continues about nephrotoxicity and relapse on ceasing to take the drug. Cyclophosphamide combined with plasmapheresis has not been shown to provide additional benefit compared with cyclophosphamide alone, and its use is now limited to patients who develop a thrombotic thrombocytopenic purpura-like illness or who have disease highly resistant to treatment.³⁹

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