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# Update

JAN 1991  
Vol. 9, No. 4

## **Tracking and treating lupus — the great imposter**

by *Brian L. Kotzin, M.D.*

*Systemic lupus erythematosus (SLE) is a particularly challenging rheumatic autoimmune disease because of its ability to occur in almost any system of the body.*

In fact, SLE symptoms mimic so many disorders that this malady has been misdiagnosed as everything from rheumatoid arthritis to schizophrenia. Joint pain and overwhelming fatigue are common, and irreparable damage to the kidneys, central nervous system or brain can sometimes occur.

Although a definitive cure has not yet been discovered for SLE, this chronic inflammatory illness generally has a positive prognosis, and proper medical treatment allows most victims to lead normal lives.

### **History**

"Lupus" is named for the characteristic bright red rash that spreads across the bridge of the nose and cheeks. This facial hallmark — caused by sensitivity to sunlight —

is said to resemble the markings or the bite of a wolf. The rash also can appear to have the shape of a butterfly.

SLE was once thought a rare condition, but recent studies indicate it is more prevalent than muscular dystrophy, multiple sclerosis, cerebral palsy, cystic fibrosis or leukemia. It is estimated to afflict more than one-half million Americans; 90 percent of these are women in their childbearing years.<sup>1</sup>

### **Etiology**

The specific cause of SLE is unknown, but the primary disease mechanism appears to be the production of abnormal antibodies by B lymphocytes.<sup>2</sup> It is believed that certain B cells are stimulated by helper T cells, which results in auto-antibody production and damage to healthy self-tissue.

Earlier research, now given less weight, also points to a defect in the production or function of suppressor cells, which alters the normal functioning of the immune system.<sup>3</sup> Normally, suppressor T cells help control

*Rheumatologist Brian L. Kotzin, M.D., spearheads the significantly expanded adult clinical programs in lupus and rheumatoid arthritis at National Jewish. Dr. Kotzin also conducts extensive research on lupus disease processes at the cellular and genetic levels.*

the production of antibodies by B cells. In lupus patients, however, this suppression mechanism may malfunction, allowing the production of self-damaging antibodies.

The onset of SLE occurs when its genetic predisposition is acted upon by environmental influences. Although the trigger for the illness has not been clearly defined, a virus

is a likely culprit. Once SLE is activated, female reproductive hormones also appear to play a role in determining its onset.<sup>3</sup> So do environmental factors such as bacterial infections, exposure to sunlight and emotional stress. Injury, surgery, exhaustion, nervous tension and certain drugs and chemicals all have been identified as possible precipitating factors.

## Symptoms & Diagnosis

SLE can be difficult to diagnose because its symptoms often are vague, transient and mimic other illnesses. A patient with suspected SLE requires a comprehensive review of his or her entire medical history. The disease may strike at any age, but most patients with lupus will develop it as young adults.

Symptoms usually depend upon the organs involved, and different organs may be affected as the disease runs its course. A variety of clinical features are used for classification,<sup>4</sup> including:

- discoid rash,
- malar rash,
- photosensitivity,
- mouth sores,
- arthritis,
- pleuritis or pericarditis,
- more than 0.5 of protein in urine per day or urine casts
- seizures, psychosis or cranial neuropathies,
- low white blood count, low platelet count or hemolytic anemia,
- antibody to DNA or to Sm antigen or LE cells or false-positive syphilis test, and
- abnormal titre of antinuclear antibody (ANA).

Additional lupus symptoms include fever, fatigue, weight loss, hair loss, Raynaud's syndrome (blanching of hands and feet after exposure to cold) and clinical depression.

## Research offers new clues to lupus

National Jewish immunologists and rheumatologists are continually working on understanding lupus and finding better treatments for it.

Numerous Center efforts in basic research are aimed at understanding T-cell development and how these vital components of the immune system respond to foreign invasion. This knowledge is instrumental in discerning how T cells malfunction in rheumatic diseases.

In applied research, Brian Kotzin, M.D., and Edward Palmer, M.D., Ph.D., study the genetic and cellular basis of lupus. This team has spent several years identifying and mapping one HLA gene that contributes to the illness in an animal model. They are now mapping a second gene causing the autoimmune defect.

In addition, Dr. Kotzin and collaborators have identified certain antibody-producing B cells that malfunction in autoimmunity. "A crucial question is how helper T cells stimulate certain B cells to inappropriately produce antibodies to self," Kotzin said. The researchers are designing a therapy for mice to selectively turn off B cells making destructive antibodies, while allowing the rest of the immune system to function normally. If successful, the next step would be to design a similar therapy for humans.

To further understand the genetic component of lupus, Dr. Kotzin follows about 50 adult patients in the National Jewish clinic, including several families with multiple members affected.

In a different area, Dr. Kotzin has determined that severe depression and other psychiatric symptoms sometimes associated with lupus may be caused by an antibody. Ninety percent of lupus patients with severe depression have this antibody, which suggests that people with disease-caused depression are a distinct group from those with reactive depression.

ANA (antinuclear antibodies) titers are positive in up to 98 percent of lupus patients.<sup>5</sup> However, these autoantibodies are not necessarily specific for SLE, and ANA titer should not be used as a guide for therapeutic decisions.<sup>6</sup> In addition, a small percentage of healthy people run elevated titers.

Another important laboratory abnormality in lupus patients is the production of anti-DNA antibodies. The detection of these antibodies in serum is much more specific for lupus.<sup>7</sup> Specific antibodies to other nuclear antigens (for example, to Sm, RNP, histone, etc.) can be tested

as well and can be extremely helpful in diagnosis.

These tests are complex and require expert interpretation. A number of commonly prescribed medications such as procainamide, hydralazine, isoniazid, methyl dopa and thiouracil can cause false ANA positives.

Lupus also can create an antibody to cardiolipin, which can produce a false positive blood test for syphilis.<sup>7</sup> This finding, often detected during a premarital examination, may be the first marker of lupus, preceding other symptoms by years. Antibodies to cardiolipin have been

associated with clotting problems, thrombocytopenia and certain forms of CNS disease in lupus.

### **Management and Treatment**

The management of SLE is complicated by extreme variability among patients in clinical presentation, course of disease and response to therapy. Treatment of lupus must be tailored to the individual patient and depends on the organ systems involved and the severity of involvement. The goal of therapy is to suppress disease manifestations while minimizing the cumulative toxicity of therapy, especially corticosteroids.<sup>6</sup>

While outcome in SLE has been steadily improving the last 30 years, overaggressive treatment, especially with corticosteroids, has clearly contributed to an increased number of infectious deaths. Therefore, the possibility of infection always should be considered and must be excluded prior to institution of corticosteroids or cytotoxic drugs.<sup>6</sup>

Many disease manifestations can be treated with mild forms of therapy, including a regimen of rest, exercise, relaxation/stress management and avoidance of sunlight and other contributing factors.

Education and, as required, professional counseling, also are vital parts of the patient's treatment program. The patient must become familiar with the nature of the disease, recognize the early symptoms and understand that regular medical care is essential.

### **Systemic Symptoms**

Fatigue, malaise, anorexia, weight loss and fever are common in SLE. Therapy usually depends on other organ involvement. Symptoms usually respond to conservative measures and antipyretic therapy. Rarely, patients with debilitating systemic symptoms will require corticosteroids.

### **Arthralgia/Arthritis**

Joint disease often found in lupus can produce considerable synovitis, swelling and inflammation, but rarely is destructive or deforming. Therapy includes salicylates and/or other NSAIDs. Some patients will show marked improvement in their arthritis after hydroxychloroquine therapy.

### **Dermatologic Manifestations**

Cutaneous disease in SLE frequently includes the classic malar (butterfly) rash, localized maculopapular eruptions, discoid lesions, photosensitive skin eruptions and alopecia. Localized, self-limited disease can be treated with topical corticosteroid preparations; more extensive disease may respond to hydroxychloroquine.

### **Serositis**

Pleuritis and pericarditis are common in SLE, but complications such as tamponade are rare. Patients frequently benefit from NSAIDs, e.g., indomethacin. Occasional patients may require moderate doses of corticosteroids.

### **Renal Disease**

The presence and degree of kidney involvement is the most important determinant of prognosis in SLE.<sup>8</sup> Clinical evidence of lupus nephritis is present in over 50 percent of patients, but the extent of damage varies considerably. Many aspects of management of lupus nephritis are controversial, including the clinical value of renal biopsy, the use of certain serologic correlates of renal disease activity and drug therapy. Initial treatment in most patients can be started without a renal biopsy.<sup>6</sup>

Not all patients with lupus nephritis need to be treated aggressively with corticosteroids and/or cytotoxic drugs. Initial therapy should be tailored to the clinical severity of involvement. However, patients with active lupus nephritis and severe clinical manifestations should be treated

vigorously with high-dose corticosteroids as the first-line therapy.

The most commonly studied cytotoxic regimens in lupus nephritis have been oral azathioprine, oral cyclophosphamide and intermittent intravenous cyclophosphamide. These drugs are always given in association with a dose of prednisone and should be reserved for patients with severe, refractory disease because of their relatively unknown benefits and known toxicities.

### **Central Nervous System Involvement**

CNS involvement in SLE may result in markedly different clinical presentations, and therapy should be individualized. Always rule out other causes (especially infection) of a CNS problem in the setting of SLE. The most common CNS problems are psychological, including psychosis. Headaches are common, and seizures, single and multiple, may occur. More serious CNS problems with SLE include aseptic meningitis, hemiparesis, organic brain syndrome, dementia and coma.

Other conditions related to SLE can include acute pneumonitis, pulmonary hemorrhage, interstitial lung disease, hematologic involvement, thrombocytopenia and leukopenia.

Some SLE patients require only salicylates or other nonsteroidal anti-inflammatory drugs to control pain and swelling. However, NSAIDs can cause decreased renal function, so this should be checked periodically. Antimalarial drugs, such as hydroxychloroquine, also can be useful in SLE patients. However, long-term therapy can cause retinal damage, so patients should be examined by an ophthalmologist every six months.

Dermatologic manifestations in SLE can be treated with topical corticosteroids, while antimalarial drugs are often extremely useful for

patients with more extensive skin disease.

Patients with severe SLE conditions should be treated with high-dose corticosteroid therapy. Corticosteroids, which are critically important in the management of internal organ involvement, limit abnormal antibody damage through their potential inflammatory activity, and, at higher doses, act as an immunosuppressant.<sup>9</sup>

However, the toxicity of continuous high-dose corticosteroid therapy is cumulative and severe, which

*For consultation about lupus (or suspected lupus) patients with difficult management aspects, call Dr. Kotzin at 1-303-398-1876.*

makes their prolonged use problematic. Perhaps most serious of the well-documented side effects is the associated immune suppression and increased susceptibility to severe infections. These unwanted effects sometimes can be mitigated by alternate-day drug therapy, but this approach usually is not successful in suppressing severe disease activity. Treatment must be individualized.

Cytotoxic immunosuppressants, such as cyclophosphamide and azathioprine, can be effective adjuncts in the management of patients. Promising new therapies under investigation include intravenous cyclophosphamide combined with steroids, radiation and monoclonal antilymphocyte antibodies.

### **Prognosis**

Managing lupus is a complex task involving a lot of medical decision-making. However, significant progress has been made in diagnosis and treatment, and the prognosis for

*(Continued on page 5)*

## **National Jewish experts help cut referral red tape**

As third-party payers work to control costs through managed care and other methods, referral of a patient to a specialty center can sometimes be a time-consuming hassle for primary care physicians.

At National Jewish, we do everything we can to make the referral and admission process short and simple.

In fact, many years of working closely with insurance companies, HMOs, PPOs and government agencies — virtually all types of third-party coverage — have given the specialists at National Jewish ample experience to expedite the process.

Our medical staff will review the medical information you provide for appropriateness of referral and determine with your input whether your patient should be treated as an outpatient or inpatient. Specially trained personnel at the Center handle all insurance matters, including verification of coverage and pre-certification.

In cases where insurance carriers require involvement of the referring physician for prior authorization, Admissions Department staff familiarize themselves thoroughly with the specific procedures to be followed, guide you through the process and see that minimal demands are made on your time.

Outcomes data indicating the efficacy and cost effectiveness of the Center's clinical programs, along with particulars of the patient's history, usually provide convincing evidence to the insurance carrier that referral is desirable and should be reimbursed.

Our Utilization Review Nurse Coordinator and, as necessary, our attending physicians will stay in

contact with the insurer at prescribed intervals during your patient's stay. Close monitoring of each patient's progress insures that treatment programs are appropriate and thorough, and that the patient's financial concerns are not overlooked.

If you have a patient that may be appropriate for National Jewish, please allow us to assist you any way we can with reimbursement issues. Our understanding of the kind of information insurance carriers need and our commitment to streamlining the process mean a more efficient use of your time and a more satisfactory result for your patient and his or her payer.

Remember, when it comes to insurance matters, we speak the language every day.

# Lab precisely measures immune functions

*The M. Ronald and Myrna Ruskin Clinical Immunology Diagnostic Laboratory, located at National Jewish, is one of the country's leading resources for the development and performance of specialized tests to measure immune system function.*

*Under the direction of Ronald J. Harbeck, Ph.D., and Patricia Giclas, Ph.D., the Ruskin Laboratory performs ANA testing to help physicians diagnose lupus. Also available is the more extensive ANA profile which includes anti-ds DNA, anti-Sm, RNP, SS-A and SS-B.*

*It is possible to run all tests with a minimum of one milliliter of serum. The serum should be sent to the laboratory as soon as possible after obtaining. To protect the specimen against excessive heat and cold, it should be shipped to the lab in a styrofoam container and be received at the lab within one week after being drawn.*

*It also is safe to freeze the sample and ship it to the lab packed in dry ice. It is important to pack the specimen in enough dry ice to keep it frozen until it reaches the lab. Freezing and thawing can lead to the loss of the ANA reactivity.*

*Additional tests available for lupus and other autoimmune diseases include immune complexes, rheumatoid factors and complete complement system analysis. The lab also performs a wide range of diagnostic assays for a variety of illnesses including chronic obstructive pulmonary disease, interstitial lung disease, hypersensitivity pneumonitis and cystic fibrosis.*

*Physicians nationwide look to the lab to perform specialized tests not available on a local level. In 1988, the Ruskin Lab received more than 1,500 requests from outside clients. All laboratory testing follows strict quality control for which the lab is renowned. In addition to the more than 50 specialized tests now available, Drs. Harbeck and Giclas develop new testing procedures to answer specific questions posed by physicians.*

*To share their knowledge of immunological assay methods, Drs. Harbeck and Giclas are writing a procedures manual for all assays now available in the lab. It will be published by Raven Press early next year and will become a standard reference guide for other medical laboratories worldwide.*

*For more information, call the lab at (303) 398-1344, Dr. Harbeck at (303) 398-1337 or Dr. Giclas at (303) 398-1217. To schedule a test, contact Jeri Teague at (303) 398-1367.*

## Tracking...

*(Continued from page 4)*

most patients is quite good. Symptoms can be well controlled medically, and long-term survival with a normal lifestyle is the rule.

Unfortunately, lupus can be incredibly capricious in its presentation and its course. Symptoms may disappear for no apparent reason, and the disease may remain in remission for weeks, months or even years, only to flare up again unexpectedly.

Some people have a serious, uncontrollably progressive disease that results in renal failure and death. Other patients have very mild forms of skin and joint disease and do well throughout their lives. A lot of people in the middle have intermittent exacerbations of varying severity.

Lupus can be frustrating for both physician and patient, because of difficulty in diagnosing and an uncertain course. This is where utilizing the specialized expertise of the rheumatologist can prove invaluable. Patience and persistence, along with new research findings, can mean positive outcomes in most cases. □

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### **Daily CME Conferences**

Daily continuing education conferences on pulmonary and immunologic topics are conducted at National Jewish in Heitler Hall. All physicians in the community, as well as those visiting Denver, are welcome to attend. For information about specific topics and times, call (303) 398-1380.

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