CHAPTER 22

SYSTEMIC LUPUS ERYTHEMATOSUS

Sanford S. Hartman, M.D.

Systemic Lupus Erythematosus (SLE or lupus) is an interesting disease which can range from merely being a bother, to being a killer. Its manifestations are protean and it is very unusual for any two lupus patients to have similar stories. It is fascinating to hear two lupus patients discuss their diseases with each other, in that most of the time one would think the patients are discussing different diseases. This writing will describe many of the disease manifestations, try to give insight into how best to make the diagnosis, and briefly discuss the forms of treatment.

Lupus is probably the prototypic autoimmune disease. There is the production of autoantibodies aimed at various components of the cell nucleus (and probably other cell components as well), and the disease is associated with a wide spectrum of clinical manifestations. The heterogeneity of clinical expression is as much a focus and puzzle of research as is the pathogenesis of the auto-immune mechanism. Whether this is a single disease with multiple presentations or a group of related conditions remains uncertain.

Some things are known, however. Lupus is primarily a disease of young women (female:male ratio ranges from 5:1 to 9:1), with onset usually between 15 and 40 years of age. It has been reported at both ends of the age spectrum with the female:male ratio more closely approximating 2:1 at the extremes. In the United States, lupus occurs more frequently in Blacks and Hispanics, and there is unquestionable familial aggregation, though most cases are sporadic. Lupus is also found to coexist in extended families with other so-called autoimmune diseases such as thyroiditis and immune/idiopathic thrombocytopenic purpura (ITP). Additionally, there is concordance in a significant but minority proportion of monozygotic twins. The presence of major histocompatibility complex (MHC) gene markers provides some evidence of genetic susceptibility, and the human leukocyte antigens (HLA) DR2 and DR3 increase the relative risk of lupus by a factor of two to five.

The production of self-directed antibodies is the immunologic hallmark of the disease. While anti-nuclear antibodies (ANA) are the best characterized, there may also be antibodies directed at other molecules such as coagulation factors. The list of anti-nuclear antibodies is extensive (Table 1 is a partial list), and the immunopathogenesis of each is beyond the scope of this article, but there are two ANAs that are virtually limited to SLE, anti-double stranded DNA (anti-dsDNA) and an RNA-protein complex called Sm (named for Mrs. Smith, the first patient in whom it was found). The former is more likely to fluctuate over time and is or may frequently become negative in lupus patients, while the latter commonly remains constant and is far more likely to be positive in black than in white patients. Other ANAs are found in lupus patients but are not unique for lupus, and the so-called ANA test is diagnostic of absolutely nothing, but is an excellent screening device (many false positives, few false negatives). While ANAs are an integral part of the disease process, there is no good understanding as to why their presence may be associated with any symptoms or finding at all, why some patients and/or organs are protected from their effects and others are not, and whether this is the only autoantibody system present or active in the disease process.

CLINICAL FEATURES

The most recognized clinical feature of SLE is the "butterfly" rash, often precipitated by exposure to sunlight (photosensitivity), but the most common presenting symptom is arthralgia (about 80%). The most frequent "anytime" symptoms are skin involvements of any variety, constitutional symptoms, and arthralgia (all more than 80%). Skin manifestations, in addition to the "butterfly" rash, include discoid lesions (may be found with or without any systemic manifestations of disease), subacute cutaneous lupus erythematosus, and alopecia (diffuse or patchy).

Arthritis or arthralgias are most frequently found symmetrically and in small joints, much like rheumatoid arthritis (RA), but unlike RA, the

Table 1

ANTI-NUCLEAR ANTIBODIES

Name	Associations*
Anti-double stranded DNA (anti-dsDNA)	SLE; lupus nephritis
Anti-single stranded DNA (anti-ssDNA)	linear scleroderma
Anti-histone	drug-induced lupus
Anti-RNP	Mixed Connective Tissue Disease (MCTD)
Anti-Sm	lupus, especially in blacks
Anti-SSA/Anti-Ro	Sjogren's Syndrome; neonatal lupus syndrome; SLE; subacute cutaneous lupus
Anti-SSB/Anti-La	Sjogren's Syndrome;SLE; neonatal lupus
Anti-centromere	CREST form of scleroderma
Anti-topoisomerase I (formerly anti-Scl-70)	systemic form of scleroderma
Anti-PM/Scl (formerly anti-PM-1)	polymyositis-scleroderma overlap
Anti-Jo-1	polymyositis with interstitial lung disease & Raynaud's
Anti-Mi-2	classic dermatomyositis
Anti-Ku	scleroderma-polymyositis overlap; SLE; Graves' disease
Anti-ribosomal-P	neuropsychiatric lupus
Anti-cardiolipin	recurrent miscarriage; thrombocytopenia; DVT; stroke (arterial or venous)

*These are associations only and are only relatively specific. There is frequent overlap both in regard to diseases and antibodies; some are more sensitive, others more specific.

arthritis is rarely erosive or destructive, although deformities may occur (Jaccoud's arthritis). Symptoms referable to the kidney are rare, but renal involvement is found frequently by the presence of proteinuria, casts of different types, hematuria, pyuria without infection, or elevated serum creatinine. There are various morphologically different features noted on renal biopsy, the most commonly described being mesangial, membranous, focal proliferative, diffuse proliferative, and mixed. Diffuse proliferative glomerulonephritis (DPGN) has the worst prognostic significance. Neuropsychiatric manifestations run the gamut from headache to central nervous system (CNS), cranial and peripheral neuropathies, and from neuroses to psychosis and severe depression. Serositis is also commonly found in SLE, with pleuritis being more common than pericarditis or peritonitis. The clinician must always be alert to the possibility of such symptoms being either on the basis of an infection or the disease itself–the differentiation being critical.

Although the most common clinical findings have been described previously, lupus patients also manifest many other types of systemic involvement including gastro-intestinal (abdominal pain, nausea, anorexia, inflammatory bowel disease, pancreatitis, liver enlargement), pulmonary (pulmonary hemorrhage, pulmonary hypertension, pneumonitis), cardiac (myocarditis, endocarditis, coronary artery disease), skin (palpable purpura, digital ulcerations, urticaria, livedo reticularis, subcutaneous nodularities), and reticuloendothelial (lymphadenopathy and splenomegaly). Many of the diffuse manifestations of SLE are on the basis of vascular involvement, i.e., vasculitis.

Antinuclear antibodies have been mentioned earlier. Additionally, there are many other laboratory abnormalities in lupus, some very non-specific, such as anemia, an elevated sedimentation rate (ESR) or C-reactive protein (CRP), and others a bit more typical but also certainly not specific (see Table 1 regarding ANAs). This latter group includes thrombocytopenia, leukopenia, false positive VDRL, hematuria, proteinuria, active urinary sediment, lupus anticoagulant, hemolytic anemia (frequently but not always Coombs positive), and hypocomplementemia. Some are rather prognostic such as the combination of thrombocytopenia, false-positive VDRL, and lupus anticoagulant,

which not infrequently accompanies the anti-cardiolipin antibody syndrome, or the presence of positive anti-dsDNA antibody and hypocomplementemia, which frequently is associated with active renal disease.

LUPUS IN PREGNANCY

A discussion of lupus would be incomplete without at least touching on two other aspects of the disease; i.e., lupus in pregnancy and drug-induced lupus. While lupus does not interfere with the ability to conceive (fertility rates are normal), the lupus patient has a significantly reduced chance of carrying to term whether from intrauterine death, prematurity, or spontaneous abortion. The latter is not uncommonly associated with the anti-cardiolipin antibody syndrome (positive anticardiolipin antibody, increased incidence of miscarriage, deep vein thrombophlebitis [DVT], and stroke [arterial or venous] as well as thrombocytopenia). There is also an increased incidence of "therapeutic" abortions in SLE, probably for psychosocial reasons. It had previously been felt that lupus was more likely to flare during pregnancy, but that now appears to not be the case. Finally, many of the manifestations of toxemia of pregnancy are similar or identical to active lupus renal disease and differentiation is critical.

Treatment of lupus during pregnancy may include salicylates (until 7 to 10 days before delivery) and especially corticosteroids. Less than 60 mg/day of prednisone is probably effectively metabolized by the placenta and so will not likely affect the fetus, but the fluorinated steroids do cross the placenta and their use is dependent upon whether it is felt beneficial to treat the fetus with steroids, such as in cases of fetal distress or congenital heart block.

DRUG-INDUCED LUPUS

Drug-induced lupus (DIL) was first described more than 50 years ago (from sulfadiazine) and since then more than 70 drugs have been implicated, the strongest evidence existing for hydralazine, isoniazid (INH), methyldopa, d-penicillamine, procainamide, and quinidine. The incidence of drug-induced diseases is a function both of dose and duration of treatment, the latter usually requiring at least a year of exposure. Musculoskeletal, cutaneous, constitutional, and pleuropericardial symptoms are most common in DIL, while renal, neuropsychiatric, and vasculitic involvement are fairly uncommon. While anti-histone antibodies are quite common in DIL (>95%), they are also quite frequently found in SLE (about 70%) in general. ANA induction by many drugs is found far more frequently than frank DIL.

TREATMENT

In most instances, the treatment of lupus is governed by the specific manifestation. Prophylaxis is quite important (e.g., the avoidance of sunlight or fluorescent lighting in photosensitive individuals, or the avoidance of known infection risks by such measures as yearly influenza vaccination).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used especially for musculoskeletal symptoms, serositis, and constitutional symptoms, though they need to be monitored closely or avoided in patients with renal dysfunction.

Corticosteroids are used for a plethora of reasons in a myriad of dosage regimens, and are both credited for life-saving in many patients and for life-shortening in others (elevates cholesterol, blood pressure, glucose levels, weight, increases susceptibility to infections, increases incidence of osteonecrotic fracture, especially hip, and so forth).

Antimalarials (hydroxychloroquine, chloroquine, quinacrine) are particularly helpful for cutaneous and musculoskeletal involvement as well as for constitutional symptoms, and low-dose methotrexate (7.5 to 15 milligrams per week) may be a reasonable alternative to it.

Dapsone is helpful in several varieties of cutaneous lupus (50 mg per day with gradual increase to no more than 150 mg per day) but may be associated with dose-related hemolysis, especially in those with G6PD deficiency.

Azathioprine (1 to 2 milligrams per kilogram per day) is used especially in patients with lupus renal disease, but must be monitored carefully for bone marrow toxicity, and may increase the risk of hematopoietic or lymphoreticular malignancy.

Cyclophosphamide is the most studied and widely used nitrogen mustard alkylating agent, and has found extensive use in aggressive lupus renal disease. However, its use is fraught with extensive toxicity potential, including nausea, vomiting,

alopecia, marrow toxicity, risk of infection, teratogenicity, ovarian failure, azospermia, damage to bladder mucosa, and hematopoietic and lymphoreticular malignancy.

Lupus thrombocytopenia frequently responds well to the androgen danazol, but may not be used in pregnant or breast-feeding women or in those with unexplained vaginal bleeding. Liver or renal dysfunction are relative but not absolute contraindications. Other therapies under investigation include cyclosporin A, use of immune globulin, plasma exchange, and total lymphoid irradiation.

CONCLUSION

It is obvious that lupus is a complicated disease about which much is known but far more is yet to be learned. Its protean presentations and manifestations are fascinating yet frustrating. Its treatment represents a bit of symptomatic relief coupled with attempts at immuno-manipulation and probably a touch of alchemy as well. Lupus is common enough that the generalist will not infrequently encounter it but elusive enough that it may go unrecognized for long periods of time. Like with any other medical challenge, the diagnosis will never be made unless and until it is considered, and even then it remains a challenge to successfully confront the everyday medical issues in this immuno-compromised individual.

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Appendix 1.

1982 Revised Criteria for Classification of Systemic Lupus Erythematosus*

1.	Malar rash	so-called "butterfly rash", tends to spare nasolabial folds
2.	Discoid rash	raised patches with keratotic scaling, follicular plugging, atrophic scarring
3.	Photosensitivity	skin rash as result of reaction to sunlight
4.	Oral ulcers	oral or nasopharyngeal ulceration, usually painless
5.	Arthritis	peripheral joint non-erosive arthritis with tenderness, swelling, effusion
6.	Serositis	pleuritis or pericarditis
7.	Renal disorder	persistent proteinuria (>0.5 Gm or 3+) or cellular casts
8.	Neurologic disorder	seizures or psychosis without other known cause
9.	Hematologic disorder	hemolytic anemia (with reticulocytosis) or leukopenia (<4000) or lymphopenia (<1500) or thrombocytopenia (<100,000)
10.	Immunologic disorder	positive LE preparation or anti-DNA or anti-Sm or false positive STS
11.	Antinuclear antibody	positive in the absence of known ANA inducing drugs

*4 or more of the eleven criteria required serially or simultaneously