Systemic Lupus Erythematosus and Related Syndromes

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1. Systemic Lupus Erythematosus (SLE)

Introduction and Epidemiology

Lupus is a multisystem autoimmune disease characterized by the production of antibodies and cells directed against many subcellular components and whole tissues. For reasons that are not understood, there are arrays of antibodies directed against specific molecules of nuclei and cytoplasm.[1] These specificities are often against highly conserved antigens like native DNA.

Lupus affects both sexes but young women between the ages of 15 and 40, the childbearing years, are primarily affected. There is a female-to-male ratio of 10 to 1[2] and most cases occur during these years. However, lupus can involve any age group. Although men with lupus are fewer in number, there is no difference in clinical presentation between the genders. The disease is not limited to the childbearing years and can begin anytime during early childhood or in the later years and the sex ratios vary depending on age. In early childhood, the ratio of females to males is approximately 4:1, whereas in later life this ratio approximates 8:1.

The prevalence of lupus also varies with ethnicity and is more common in African Americans, Asians, and Latinos where the prevalence is approximately 1 in 250 to 1 in 500.[3,4]

A recent study by Uramoto, et al[6] in Olmstead County, Minnesota showed that the incidence of SLE has tripled over the past four decades. Using 1982 criteria (ACR), the estimated incidence of SL (adjusted to the 1970 population) in the white population was 5.56/100,000 between 1980-92, compared to 1.51/100,000 between 1950-79. Two recent United States studies based on random telephone interviews resulted in a prevalence of 124/100,000 (Confidence intervals 40, 289).[7]

As a multisystem disease, lupus affects any or all systems of the body. There is a higher frequency of the disease among the first-degree relatives of patients. In extended families, the disease coexists with other autoimmune conditions such as autoimmune hemolytic anemia, thyroiditis, and idiopathic thrombocytopenic purpura (ITP) and diseases that have no known autoimmune basis like fibromyalgia. Lupus is related to genes of the MHC class II and III on chromosome 6. However, some forms of familial lupus are associated with constitutive genes located on chromosome 1.[8] Lupus is not inherited in a typical Mendelian manner.[9] SLE occurs in approximately 25% to 50% of monozygotic twins and 5% of dizygotic twins.[10] Despite the fact that this disease can occur in families, most cases are sporadic. Numerous MHC genes are associated with the disease (see below).

Classification Criteria

ACR criteria for the classification of the SLE patient were updated in 1997. "Positive LE cell preparation" was omitted and the description of the antiphospholipid syndrome and standardization of the techniques for anticardiolipin and lupus anticoagulant were included. The false positive syphilis test has been expanded to the finding of antiphospholipid antibodies.[11]

Immunopathology

There is no known etiology of lupus despite an extensive search for a viral, bacterial, or chemical cause.

The pathophysiology of lupus involves the immune and other systems. The principle clinical manifestations of this disease are inflammation, the premature infarction of blood vessels, vasculitis, and immune complex deposition in a variety of organs. Such deposition is associated with considerable morbidity.[12] The most intensively studied organ of the lupus patient is the kidney (see below). The results of the autoimmune processes are the various pathological changes found within the kidney. These include increases of the mesangial cells and the mesangial matrix, the accumulation of inflammatory cells, basement membrane abnormalities, and immune complex deposition.

Many other organs are affected in lupus patients and nonspecific inflammation is the hallmark of the disease. Because the deposition of immune complexes which are large in number vary from individual to individual, pathology can range in severity from mild to severe depending on organ involvement. On occasion, thromboses can occlude vital vessels that supply blood to various organs resulting in macro- or micro-infarcts. The origins of these thrombi are complex and can be the result of a vasculitic inflammatory process or the phospholipid directed antibodies that cause a pro-coagulant state. The pathology is complex

because other autoantibodies are often found and can contribute to vascular lesions. One example of this is the anti-endothelial antibodies that are part of the pathogenesis.[13]

There are many aspects of the disease that remain unexplained, among these are the accelerated atherosclerosis with an extraordinary risk for cardiovascular disease in young people[14] and severe osteonecrosis.[15] It is unclear whether these two associated phenomena are the result of a disease process or the treatment of the disease with drugs like the corticosteroids.

The main laboratory findings in this disease include aberrant cell populations directed against autoantigens and a plethora of different autoantibodies.[16] The antibodies found in this disease are directed to a host of self-molecules that are found in the nucleus and the cytoplasm as well as the cell surface. Lupus sera can also contain antibodies to histocompatibility markers as well as clotting factors. At any one time, a lupus patient can have high titers of antibody to antigens shared with other well described autoimmune diseases such as the anti-Ro (SSA) or La (SSB) found in Sjögren's syndrome or the antihistone antibody found in drug-induced disease.

The antibodies directed against components of the cell nucleus are called antinuclear antibodies or ANA. Patients with lupus can be ANA negative, but these are usually the result of a poor substrate for staining, erroneous interpretation of the test[17] or aggressive therapy resulting in a transient depletion of antibody. There are many antigens within the cell that can become targets for autoantibodies. Many of these autoantigens like DNA or RNA are highly conserved among mammalian species. Formerly, the use of ANA patterns aided in the diagnosis of the disease, however this is not the case today.[18] Only the nucleolar and centromere (ANA) patterns of staining are used, since they are associated with scleroderma, MCTD, or CREST syndromes that differ from SLE.[19]

Most autoantibodies are not useful in following the prognosis or activity of the disease. Only two antibodies, the Smith (Sm) and the anti-native DNA antibody are specific to patients with lupus.[20] These two autoantibodies differ in their patterns of expression, clinical association, sensitivity and specificity. While anti-DNA levels may fluctuate with disease activity, anti-Sm activity remains constant during the course of the disease. Anti-DNA antibodies are particularly useful in following the course of renal disease in patients with lupus.[21] Generally disease activity can be measured accurately through measurement of the native DNA titer and the total hemolytic complement, or the measurement of specific components like C3 and C4.

Many antibody systems are associated with disease classification, and include the antibody to ribosomal P proteins and psychiatric disease;[22] antibodies to Ro with neonatal lupus,[23] and subacute cutaneous lupus;[24] antibodies to phospholipid with the thrombosis of blood vessels; and antibodies to blood cells with resulting hemolytic anemia.[25] Most attempts to associate other antibodies with system involvement and disease manifestations have not been successful. A concerted effort to identify biomarkers for both the easy diagnosis and clinical management of lupus patients is a priority for the research establishment.

Heredity and SLE

There are many determinants of disease activity within the immune system. The development of SLE has a strange genetic basis.[26,27,28] Both exogenous and endogenous factors can trigger the disease lupus, but the predisposition to this disease is clearly inherited. However, the origin of lupus is likely to be multigenic and involve different sets of genes in different individuals.[8] On human chromosome 6, there are a variety of genes which comprise the mixed histocompatibility complex (MHC). Population based studies indicate that susceptibility to SLE involves class II gene polymorphism. An association of HLA DR 2 and DR 3 with SLE is commonly found. Presence of these alleles confers a risk of two to five for lupus.[27] Class II genes also exert a decisive influence on the production of a particular ANA.[29] There is various class II specificity found within the response genes.[28] Inherited complement deficiencies (MHC Class III) also influence disease susceptibility in a manner that is not clear.[30] Like class I and class II molecules, complement components, especially those within the sixth chromosome (viz, C4A and C4B), show striking genetic polymorphism. If there is a deficiency of C4A molecules—a common occurrence in the population—as many as 80% of patients will have a high-risk for developing lupus.[31,32] Systemic lupus erythematosus is also associated with inherited deficiencies

of the early components of complement C1q, C1 R/S and C2.[33] The exact mechanism involved in the acquisition of lupus from complement deficiency is not known. An attractive hypothesis is that excess amounts of antigen that cannot be cleared by a complement system defective in specific components.

Other susceptible factors involved in the acquisition of lupus include the immunoglobulin and T-cell receptor gene systems.[34] Despite these hypotheses, no known polymorphisms of the T-cell receptor have been associated with the disease. In addition, GM markers or heavy chain allotypes of immunoglobulins have not been helpful in predicting disease susceptibility.

Recent developments in the area of lupus genetics are provocative. Besides MHC Class II and III genes, variants of the Fc gamma receptor confer distinct phagocytic properties to cells in certain patients. The absence of certain alleles provides a mechanism for the acquisition of immune complex disease. When the receptor Fc gamma RIIa is present, African-Americans who would otherwise develop severe lupus nephritis achieve a certain protective effect. This determination showed that lupus nephritis increased in this population when the receptor numbers decreased. Hypothetically, this increased risk of nephritis would occur because of ineffective clearance of immune complexes.[35]

In other carefully performed case controlled studies, factors such as mannose-binding protein, IL-6, BCL-2, and IL-10[36] have been associated with lupus nephritis or SLE.

One research group suggests that autoimmunity is a Mendelian dominant trait.[37] Evidence for linkage of a chromosome 1q41-42 region with familial lupus exists and is based on murine studies of a very similar locus.[8]

Studies of lupus mice show that specific serological phenotypes did not show gender bias whereas associated clinical manifestations such as glomerulonephritis did show a gender bias. Genomic scanning of these mouse strains linked six chromosomal intervals with the expression of one or more phenotypes. These studies indicate that specific genetic pathways in mice can be associated with SLE pathogenesis.[38] In recent mouse studies, a three-step pathogenetic pathway is hypothesized: loss of tolerance to nuclear antigens, transition to autoimmunity, and end organ targeting. There may be genes for each of these steps.[39]

Gender Aspects

Fewer aspects of this disease are as impressive as the large female prevalence. Approximately 10 females are affected for every male after puberty. The reasons for this skewed sex effect are unknown. Various theories have been provided which include abnormal sex hormone metabolism[40,41,42] and the effect of sex hormones on the immune system.[43] Where T-cells are grown in the presence of estradiol, calcineurin steady state mRNA and phosphatase activity increase. This increased activity is only seen in SLE females and not normal females.[44] Observations from both humans[45] and animals[41,42] showing that sex steroids affect immune function provides the basis for the use of androgens like DHEA in the treatment of SLE.[46,47,48] It is also the rationale for the avoidance of estrogen hormones in the premenopausal female. However, definitive data concerning both hormone replacement therapy and use of premenopausal oral contraceptives suggest that there are no differences between SLE and control women. Women who have antiphospholipid antibodies should not take any hormone preparations because of the increased chances of thromboses.[49,50]

Prolactin also has cytokine-like activity and is associated with a lupus-like syndrome in humans and mice. There are also other factors that can account for the skew of the female patients that have lupus.[51]

Murine Models

Murine lupus has been an interesting model for the study of human SLE. There are several strains of inbred mice with inherited lupus-like disease. These mice have been described and studied and display all the features that mimic human lupus such as the production of ANA, immune complex glomerulonephritis, lymphadenopathy, and abnormal B- and T-cell function. All of the mouse strains differ concerning certain serologic and clinical findings, as well as the incidence of the disease between the sexes. It is apparent from studies of mice that the development of a full lupus-like syndrome requires many unlinked genes.[52]

There are properties of certain mice that can promote antiDNA production as well as alter the number and functional properties of both B- and T-cells.[41,42] In mice that have the lpr and the gld abnormalities there are immunologic problems that arise from mutations of apoptotic genes.[53,54] The process of apoptosis, also known as programmed cell death, plays a major role in the development of the immune system in some murine models as well as the establishment and maintenance of tolerance. Recent investigations showed that the lpr mutations result in the absence of Fas. The Fas mutation results in the defective apoptosis of lymphocytes and apoptosis is necessary for the destruction of auto-reactive T-cells.[54] Unlike human lupus, the murine strains lack MHC class I or II markers that can be identified as susceptibility factors. One interesting aspect of the New Zealand lupus strains of mice is the low level of the pro-inflammatory cytokine TNF-alpha.[55] This absence is important because reconstitution of the mouse with TNF results in amelioration of renal disease.[56] Murine studies prove that a significant genetic background is necessary for the development of the disease.[57] Moreover, in mice most of the susceptibility genes needed for the acquisition of SLE are not in the MHC.[58]

A review of the murine models is important to a basic understanding of the pathogenesis of lupus. A large number of both spontaneous and induced models of lupus exist. The earliest model of this disease in mice was described in the (NZBxNZW)F1 hybrid developed around 40 years ago by Helyer and Howie. In this strain, females predominate and the usual development of lupus is progressive renal disease. In 1976 two additional models were added, which were the BXSB and the MRL strains.[59,60] Subsequently the MRL strains were divided into the MRL +/+ strain which developed mild lupus and the MRL lpr/lpr strains which developed a more severe form of the illness characterized by lymphoproliferation. The MRL murine disease is equally severe in both males and females whereas the BXSB murine lupus predominates in the male and is Y chromosome accelerated. There are many murine models where certain forms of lupus are induced. These models include the 16/6 and 4B4 strains which develop autoantibodies against phospholipids and other diverse antigens after immunization with autoantibody.[61,62,63] These animals are usually immunized with antibody and form anti-idiotypes. Other induced models include graft-versus-host models wherein mice are injected with parental cells and develop autoantibodies and sometimes nephritis in response to the immunization.[64]

Clinical Presentation

There are many precipitating factors involved in the exacerbation of lupus (Table 1).

There are criteria for the classification of the patient with SLE. The patient must fulfill four of these criteria to be classified as having lupus (Table 2).

Skin Manifestations

The skin is one organ system where lupus manifestations are very variable (Table 3). The skin lesions found in lupus can show inflammation in combination with deposition of immunoglobulins at the dermal-epidermal junction.[65,66,67] In these skin lesions, the deposition of immunoglobulins and complement components is reminiscent of the kidney. These immune complexes deposit in a band-like pattern and can be seen by immunofluorescent

Table 1

Precipitating Causes of Disease

Exacerbation in Lupus
Sun exposure
Ultraviolet light exposure
Infection
Emotional stress
Surgery
Pregnancy
Abortion
Sulfonamides
Birth control pills (?)

Table 2

The Revised Criteria for the Diagnosis of Systemic Lupus Erythematosus*

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminence, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4.Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis: convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion OR b) Pericarditis: documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater that 0.5 g per day or greater than 3+ if quantitation not performed OR b) Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurology	a) Seizures: in the absence of offending drugs or known metabolic disorder derangement; eg, uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis: in the absence of offending drugs or known metabolic derangement; eg, uremia, ketoacidosis, or electrolyte imbalance
9. Hematology	a) Hemolytic anemia: with reticulocytosis OR disorder b) Leukopenia: less than 4,000/mm^3 total on two or more occasions OR c) Lymphopenia: less than 1,500/mm^3 on two or more occasions OR d) Thrombocytopenia: less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic	a) Anti-DNA: antibody to native DNA in abnormal titer disorders OR b) Anti-SM: presence of antibody to SM nuclear antigen OR c) Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anti-cardiolipin antibodies, 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
11. ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced" lupus syndrome

**This classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person must have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation. The modifications to criterion number 10 were made in 1997.*

microscopy.[68,69] The immune complexes are deposited in affected and unaffected skin.

The most recognized manifestation of SLE is the butterfly rash, an erythematous elevated, pruritic, ulcerated painful lesion in a malar distribution; however, the malar rash is found in only 30% of patients.[70] There are other types of lesions that are just erythematous, resembling a flush of the skin, bullous lesions, and the rash of photosensitivity that can present in many ways. A specific lesion called subacute cutaneous lupus erythematosus (SCLE)[69] is a very distinct cutaneous lesion that is nonfixed, nonscarring, and can be variable. The lesions of this particular skin disease usually occur in sun-exposed areas as either a papulosquamous variant or annular lesions that resemble erythema anullare.

Another skin manifestation is the discoid lesion.[70] Discoid lesions are disfiguring and begin as red papules or plaques with adherent scaly and poorly pigmented central areas. There can be scarring and central atrophy. In lupus patients, alopecia or hair loss can be diffuse or localized. While this is most common at the time of flare, it usually grows back. Another common form of skin lesion involves the mucous membranes, resulting in mouth, nasal and vaginal ulcers. There can even be erosions of the nasal septum. Other skin manifestations include purpura, nail fold and paronychial infarctions, splinter hemorrhages, and Osler's or Janeway lesions (seen in endocarditis).

Exact reasons for skin lesions in some patients are not known. There appears to be a relationship of skin lesions to apoptosis in the epidermis[71] with overexpression of Fas and reduction of Bcl-2 in basal cells.

Musculoskeletal Manifestations

The most common system affected in the lupus patient is the musculoskeletal system; arthralgias and arthritis are seen in 90% of patients as an initial complaint.[72] While lupus arthritis can involve any joint of the body, it typically involves the small joints of the hands, the wrists, and the knees. There can be symmetrical involvement; however, the arthritis can be migratory and transient or persistent and chronic. At these times, one or more joints might be severely inflamed, giving one an asymmetric appearance. Soft-tissue swelling is very common. Microscopic analysis

Table 3

Some Skin Manifestations of Lupus Erythematosus

Malar flush
Photosensitivity
Chronic discoid lesions
Non-scarring alopecia
Butterfly eruptions
Petechiae, purpura, ecchymoses
Maculopapular lesions (UV related or non-exposed)
Hypopigmentation
Urticaria
Hyperpigmentation
Pruritis
Periungual erythema
Subcutaneous nodules
Bullae
Lupus profundus
Acute cutaneous
Subacute cutaneous
Livido reticularis
Osler's or Janeway's lesions

Table 4

Factors that May Influence the Prognosis of Lupus Nephritis

General
Age
Sex
Race
Education
Clinical Aspects of Renal Involvement
Severity of illness
Disease duration
Presence of hypertension
Other organ system involvement
Renal Histology
Activity index (disease activity and severity)
Chronic index (sclerosis and fibrosis)
Location of immune deposits
Capillary thrombosis
Immunology/Pathogenetic Factors
Type of circulating immune complexes
Anti-double-stranded DNA antibodies
Complement activation
Reticuloendothelial system dysfunction
Circulating anticoagulant
Platelets
Fibrinolytic abnormalities
Specific Treatment

Table 5

Indices of Activity and Chronicity in Lupus Nephritis*

Activity Index (Range 0 to 24)
Glomerular hypercellularity
Leukocyte exudation
Karyorrhexis/fibrinoid necrosis
Cellular crescents
Hyaline thrombi
Tubulointerstitial inflammation
Chronicity Index (Range 0 to 12)
Glomerular lesions
Glomerular sclerosis
Fibrous crescents
Tubulointerstitial lesions
Tubular atrophy
Interstitial fibrosis

** Individual lesions are scored 0 to 3+ (absent, mild, moderate, severe). Indices are composite scores for individual lesions in each category of activity or chronicity. Sclerosis/karyorrhexis and cellular crescents are weighted by a factor of 2.*

of the synovium shows some inflammation. Rarely is there erosion of bone, the presence of effusion, or any kind of contraction. A particular form of unusual joint involvement in lupus is that of Jaccoud's arthropathy, a non-erosive deforming form. This form of arthritis is also found in acute rheumatic fever. Patients with lupus can have muscle aches and weakness and there can be myositis with elevations of both CPK and aldolase levels.[73]

Renal Manifestations

These immune deposits within the kidney include the immunoglobulins G, M and A as well as components of complement.[74] Deposits can be seen in the mesangial area on electron and light microscopy, and the sub-endothelial and sub-epithelial side of the basement membrane.[75,76] The pathologic findings in the kidney are classified according to a variety of schemes and biopsy can predict outcome (Table 4).[77] The World Health Organization classification (Table 6) is based on the extent and location of the similar changes within the glomeruli as well as alterations of the basement membrane. A second classification is based on an activity and chronicity score (Table 5). These two systems are extremely useful in that they predict outcome and provide a reason for biopsy of the kidney.[78,79]

All patients with lupus have immunoglobulin deposition in the kidney when examined by immunofluorescence.[75] Patients can have involvement of the kidneys

Table 6

World Health Organization Classification of Lupus Nephritis

Class of Patient	Renal Histology	Clinical Presentation	Prognosis
I. Normal	Normal	No abnormalities	Excellent
II. Mesangial Lupus Nephritis	Mesangial hypertrophy; mesangial immune deposits	Up to 25% no abnormalities; transient minimal proteinuria and/or hematuria; decreased C3, C4; and elevated anti-DNA in one-third	Good
III. Focal Proliferative Lupus Nephritis	Both mesangial and endothelial proliferation; immune deposition along capillaries and along capillary lumens; fewer than 50% glomeruli involved	Mild proteinuria (<1 gm/24 hr) and hematuria; nephrotic syndrome in 20%; decreased C3 and C4 and elevated anti-DNA in 80%	Moderate
IV. Diffuse Proliferative Glomerulonephritis	More than 50% glomeruli involved; subendothelial immune deposits; cell proliferation resulting in crescents; hematoxylin bodies present	Moderate to heavy proteinuria, hematuria with red blood cell casts, mild to severe renal insufficiency; hypertension common; decreased C3 and C4; increased anti-DNA in all	Poor
V. Membranous Glomerulonephritis	Subepithelial granular immune deposits	Nephrotic range proteinuria in 2/3 of patients; microscopic hematuria; hypertension; C3, C4 and anti-DNA normal	Moderate
VI. Sclerosing	Focal segmental and global glomerular sclerosis; fibrous crescents and vascular sclerosis	Severe renal insufficiency	Poor

to the exclusion of other manifestations. The patients may be asymptomatic and present with nephrotic syndrome or hematuria initially.[80] The presence of protein in the urine, casts, hematuria, or abnormal renal function tests require immediate investigation. The renal manifestations depend on the degree of deposition of complement and immunoglobulin. The degree of kidney involvement is determined only by renal biopsy and the long-term outcome is determined by the histology.[81,82] The overall therapy of this manifestation depends on the histology of the lesion and the activity-chronicity index.[76]

The mechanisms of renal damage are not clear; however, anti-native DNA antibodies cross-react with a glomerular structural protein in immunodeficient mice.[83] The renal histology might represent a specific cytokine profile. In one study, this was seen to be a TH1 profile when diffuse proliferative glomerulonephritis was found.[84]

Neuropsychiatric Manifestations

Neuropsychiatric manifestations occur in over 67% of patients with systemic lupus erythematosus.[85] These manifestations are associated with active disease or exist as an isolated finding. Concerning the central nervous system, the cranial and peripheral nerves and the psychiatric profile can all be uniformly affected. Patients with lupus can have intractable headaches. Migraine headaches are common, particularly in young ladies with the phospholipid syndrome.[86] Seizures, chorea and cerebrovascular accidents are also related to specific antibodies like the phospholipid antibody.[87] One helpful antibody system has been the antiribosomal P protein that has some specificity for neuropsychiatric disease.[22] The basic diagnosis, however, still depends on the MRA/MRI, CAT scan and the lumbar puncture. Organic brain syndromes of lupus are defined as states of disturbed mental function and delirium, emotional problems, impaired memory and concentration.[88] The diagnosis of neuropsychiatric lupus is very difficult and often one of exclusion. Other possible etiologies have to be eliminated. There are 19 different neuropsychiatric syndromes according to a multidisciplinary panel of ACR experts.[89]

While the diagnosis of lupus of the central nervous system is largely clinical,[90] one can find cerebral spinal fluid abnormalities such as pleocytosis or high CSF protein. These are nonspecific findings. Electroencephalographic abnormalities are also nonspecific. Radionuclide scans employing labeled oxygen and positron emission tomography (PET) are promising. Magnetic resonance imaging (MRI) can be helpful in finding small areas of increased signal intensity in both the gray and white matter.[91,92] The additional use of MRA/MRI can indicate whether microthrombi or cerebrovasculitis are the basis for abnormal clinical findings. However, the overall significance of MRI positive areas in the brain is not clear in most instances.[93,94,95,96]

Peripheral neuropathies can be motor, sensory or mixed.[93] A Guillain-Barre type of neuropathy has been described in lupus.[85] Rarer types of spinal cord involvement like transverse myelitis has also been observed in patients with and without phospholipid antibodies.

Cardiac Manifestations

Cardiac involvement in lupus varies from acute to chronic disease. The most common cardiovascular presentation in lupus is pericarditis.[97] Serositis in lupus is common and can present as pericarditis, peritonitis, or pleurisy.[98] However, the most common cause of death of lupus patients today is atherosclerotic heart disease[99] in contrast to the acute infections of several decades ago.[100] Other forms of cardiac involvement include inflammatory myocarditis and endocarditis. Severe coronary artery disease is accelerated in SLE and probably associated with the antiphospholipid syndrome (APLS). In addition, many patients present with cardiac arrhythmia[101] or conduction defects,[102,103,104,105] and SLE can mimic congestive heart failure.[106] Patients who present with pericarditis often have chest pain and congestive heart failure and the physician must consider other reasons for these symptoms. Coronary vasculitis, although not common in lupus erythematosus, has been reported in patients with the secondary phospholipid syndrome. Often it is not certain whether premature coronary death is the result of thrombus or accelerated atherosclerosis.[14,107] Valvular disease is the result of non-bacterial verrucous vegetation. These vegetations previously described at autopsy (Libman-Sacks) are now seen with frequency in patients with the antiphospholipid syndrome.[108]

Although the ultimate causes of atherosclerosis in Western society remain unclear, this phenomenon is prevalent and accelerated in the lupus patient. There are probably many reasons for this, but some that are likely to be contributing causes are the presence of antiphospholipid antibodies,[105] high levels of homocysteine, factor antibodies, and hyperlipidemia.

Pulmonary Manifestations

The presentation of pulmonary lupus (Table 7) varies and can present as pneumonitis, pulmonary hemorrhage, pulmonary embolus, and pulmonary hypertension.[109,110] A typical acute pulmonary presentation would consist of cough, fever, shortness of breath, and occa-

Table 7

Pulmonary Involvement in SLE

Pleuritis	60%
Pleural effusion	40%
Parenchymal lung-bacterial	
Parenchymal lung (lupus pneumonitis)	
Pulmonary embolus (thrombophlebitis)	
Pulmonary hemorrhage	
Pulmonary hypertension	
Restrictive lung disease	
Intimal medial thickening	
Medial hypertrophy	
Raynaud's	75%
Dyspepsia	95%
Chest pain	48%
Cough	29%
Loud P2	84%
Systolic murmur	63%
Right ventricular lift	53%
Thromboembolism	

sionally hemoptysis. In all instances, the pneumonitis of lupus erythematosus must be differentiated from classical infection.[111] Such differentiation may require broncho-alveolar lavage, the collection and culture of sputum, or in the worst-case scenario, an open lung biopsy.[112,113,114] A common presentation is that of pleural effusion. This is more commonly observed in patients with drug-induced lupus[115] and in older onset patients with SLE. Pulmonary hemorrhage presenting with hemoptysis or initially as an infiltrate is uncommon.[116] Diffuse alveolar hemorrhage has recently been reported with lupus nephritis.[117,118]

Pulmonary hypertension as a result of the antiphospholipid antibody syndrome or for other reasons cannot be distinguished from idiopathic pulmonary hypertension.[119,120] This diagnosis poses particular problems because patients present with dyspnea, a normal chest x-ray, and a restrictive pattern on pulmonary function testing. Raynaud's phenomenon is frequently present in these patients. The overall etiopathogenesis is unknown.

A rare form of pulmonary involvement with SLE is phrenic nerve paralysis,[121] which is the cause of "shrinking lung syndrome."[122]

Gastrointestinal Manifestations

The gastrointestinal manifestations of systemic lupus are common and symptoms can range from abdominal pain, anorexia or nausea, to intractable vomiting.[123] The reasons for these gastrointestinal symptoms include peritonitis, vasculitis of the bowel, pancreatitis, or inflammatory bowel disease.[124] In most patients, the peritoneal inflammation that causes acute abdominal pain will not resolve until the infusion of steroids. As with every other manifestation, patients can have chronic signs and symptoms of gastrointestinal disease with ascites and pain that resemble many other diseases. Mesenteric vasculitis generally presents with insidious lower abdominal pain that can come and go over many weeks or months.[123] This variant can often resemble intestinal ischemia. Angiography will reveal the vasculitis.[125] Overt clinical liver disease in lupus erythematosus is not common.[126] Liver enzyme elevations are associated with lupus vasculitis, or the ingestion of nonsteroidal anti-inflammatory drugs or salicylates.[127,128] Pancreatitis is quite common in lupus erythematosus and elevated amylase levels can be found.[129,130] The development of pancreatic pseudocysts in SLE is common. Immunosuppression is the therapy of choice in the control of the gastrointestinal manifestations of lupus.[131]

Reticulo-endothelial Manifestations

Splenomegaly is common in systemic lupus,[132] and atrophy of the spleen can be found as a result of frequent infections or infarctions. Lymphoma is described in lupus. Large lymph nodes can be found in patients with lupus at single or multiple sites. Repeated biopsy of these lymph nodes is unnecessary since the usual histological findings are reactive hyperplasia. Unlike Sjögren's syndrome, there is no predisposition to hematological malignancy unless the patient has been on long-term chemotherapy.

Prognosis and Causes of Death

The 10-year survival for SLE patients is 75%-85%; more than 90% of patients survive greater than 5 years. This survival depends on country of diagnosis. In Asian or African countries, the 10-year survival rates are 60%-70%. Leading causes of death are active disease in the newly diagnosed, while atherosclerosis is the cause of late deaths. Women with SLE age 35-44 had a 52-fold increased risk of myocardial infarction compared to an age-matched Framingham cohort. Higher mortality is associated with renal damage (not active nephritis), thrombocytopenia, a systemic lupus erythematosus activity index (SLEDAI) >20 and lung disease.[6,133-136]

Laboratory Diagnosis

The Laboratory Diagnosis of Lupus

Many common laboratory abnormalities are apparent before complex immunologic testing results are available. These results should suggest lupus in the context of a suspicious clinical history. The most common of these laboratory abnormalities are the cytopenias: leukopenia, anemia, lymphopenia, and thrombocytopenia.[132] There are different etiologies for these low cell counts: they can be secondary to chronic inflammatory disease, blood loss, renal disease, drug use, or simply the result of autoantibodies to a particular progenitor. Various tests such as the Coombs test, an antibody detection method, are employed to determine whether there are antibodies to cells like platelets or neutrophils. Most common to lupus is a generalized leukopenia with neutrophils ranging between 1500 and 4000 per cubic mm.[1] Lymphocytopenia can result from specific antibodies, cold or warm, to lymphocytes.[137,138] Thrombocytopenia can be associated with anemia and specific antibodies to platelet glycoprotein.[132] Thrombocytopenia is secondarily found in the antiphospholipid antibody syndrome.

There are many varieties of clotting abnormalities in lupus patients.[139] These can result from a circulating procoagulant associated with the phospholipid syndrome. Lupus anticoagulants and anticardiolipin antibodies, or those directed against negatively charged phospholipid, are associated with these clotting abnormalities.[140] Clues to the presence of these particular antibodies would be a false positive VDRL test and a prolonged partial thromboplastin time (PTT).[141]

The erythrocyte sedimentation rate can also be elevated in lupus, but since it represents plasma fibrinogen levels, it is not a very accurate measure of activity. The ESR can be normal in SLE.

The immunologic abnormalities in the lupus patient are quite curious. Clearly all cell types are involved. Immune cell disturbances promote the cellular hyperactivity that leads to hypergammaglobulinemia, increased antibody-producing cells, and heightened responses to many antigens, both self and foreign. There are many antigens in SLE. The origins of the immune responses to these antigens are not clear.

Many serologic abnormalities are possible in lupus patients. Only 3 specific serologic markers are truly useful in the management of the disease activity. Changes of these markers affect the prognosis of the disease: measurement of the total hemolytic complement, antiDNA antibody, and the antiphospholipid antibody. There are many other antibodies systems that are measured to support a diagnosis; these include antibodies to the Smith (Sm) glycoprotein, anti-RNP antibody, and the anti-Ro and anti-La antibodies. All patients with systemic lupus erythematosus should have an antinuclear antibody (ANA). If the test is negative, a method or substrate is usually suspect. There is a small group of patients who might be ANA negative[17] and the patient could become serologically negative during aggressive therapy.

A positive rheumatoid factor is not commonly found in the SLE patient and could suggest mixed connective tissue disease, CREST syndrome, or rheumatoid arthritis.

Drug-induced Lupus

A form of lupus called drug-induced lupus (Table 8) is transient and related to the ingestion of specific chemicals.[142] Patients with drug-induced disease manifest both clinical and serological signs and symptoms during the ingestion of the specific agent. The most common examples are procainamide, hydralazine, and isoniazid.[143] There are undoubtedly many other agents that are associated with drug-induced disease. When the offending agent is removed, the disease abates. The clinical features of drug-induced lupus are rarely severe. The symptoms are usually constitutional such as fever, arthritis, and serositis. Central nervous system and renal disease are rarely found.

Table 8

Some Common Autoantibodies in SLE and Drug-Induced Lupus

Condition	Autoantibody	% Positive	Comments
SLE			
	Anti-dsDNA	30-70	Associated with nephritis, marker for SLE
	Anti-SM	20-40	Marker for SLE
	Anti-RNP	40-60	Also seen in MCTD and PSS
	Anti-Ro/SS-A	10-15	Also seen with Sjögren's syndrome (sicca syndrome)
	Anti-PCNA	5-10	
	Anti-Ku	30-40	Also seen in overlap syndromes
	Anti-lamin B	5-10	Also seen in autoimmune liver disease
	Anti-ribosomal P	5-10	Associated with psychosis
	Anti-histone	30	Seen in many disorders
	Anti-ssDNA		Seen in many disorders
Drug-induced lupus			
	Anti-histone	95-100	Seen in many disorders
	Anti-ssDNA		Seen in many disorders

Recent investigation into the possible reasons for this form of autoimmune disease is important to our understanding of idiopathic lupus.[144]

The laboratory findings in this particular variant of lupus include the cytopenias, positive LE cells, a positive ANA and rheumatoid factor test.[142] Although not specific, antibodies to single stranded DNA are common, not so antibodies to double stranded DNA. In 90% of cases, antihistone antibodies are found, but they are also not specific since they are also found in the idiopathic disease. Commonly found are antibodies against histone 2A and 2B.[145]

However, the serologic abnormalities can be slow to resolve in drug-induced disease.

There are other drugs that are associated with drug-induced lupus and one of these is minocycline.[146] This drug, used for the control of acne in many young females and for the early treatment of rheumatoid arthritis, causes a form of drug-induced lupus. This form of drug-induced lupus is distinctly different from other forms of the disease. The incidence of pANCA is increased in this population. Antinuclear antibodies, anti-DNA antibodies, and the presence of an elevated CRP, distinctly unusual in SLE, are characteristic of this illness. Antihistone antibodies

are not common in this group of drug-induced patients. The illness can also be reproduced by rechallenge with minocycline.[147]

Pregnancy and Lupus

The fertility rates of patients with systemic lupus erythematosus are identical to that of the general population.[148] The lupus patient may conceive normally although she may have difficulty carrying a pregnancy to term. There are greater numbers of spontaneous abortions, premature infants and intrauterine defects.[149] Some studies have suggested that the infant mortality is related to socioeconomic status; however, it is more likely the result of factors like activity of disease or the presence of antiphospholipid antibodies.[150] Lupus tends to flare during pregnancy and the puerperium, although this depends on the activity of the disease.[151,152] Nevertheless, it is generally agreed that patients who are gravely ill before conception have a greater chance of worsening their illness than those who are stable. This is particularly true of patients with renal disease.[74,153] The definition of the lupus flare has specific importance to the pregnant female since one must differentiate lupus flare from eclampsia and preeclampsia. Both of the latter conditions are commonly found in pregnant patients with lupus.[97] Maternal flares are associated with increased prematurity and active nephritis is an independent factor for fetal mortality.[154]

Early data indicated that hormone use in the female SLE patient resulted in worsening of the disease.[155] The use of pre- and postmenopausal hormones in SLE women for either contraception or estrogen replacement is under intense current study. Current belief is that hormone replacement therapy is safe provided patients are not given excess estrogen. Premenopausal use of estrogen containing birth control in the lupus female is an issue that has been examined and the data suggest that such individuals can take these contraceptives with some degree of safety.[156,157,158]

Therapy

The treatment of lupus erythematosus depends on the extent of disease, the immunologic activity, and the specific organs involved.[159] The first line of treatment for this disease is nonpharmacological and involves bed rest. Secondly, symptoms like joint and muscle aches as well of some signs of serositis might be treated with nonsteroidal anti-inflammatory agents. (Table 9) The latter agents can have an adverse effect on renal function and might not be good for a patient with previously compromised renal function. Newer agents, which inhibit cyclo-oxygenase 2 enzymes selectively, have shown no greater promise with regard to the treatment of lupus arthralgias; moreover, there is a chance that the sulfonamide moiety on some COX2 inhibitors might exacerbate the illness. Recent data implicating selective COX2 inhibitors with new onset hypertension and acute myocardial infarction may eliminate these drugs entirely.[160]

Antimalarial drugs like hydroxychloroquine or chloroquine are extremely useful in the early management of mild to moderate disease. These drugs act as lipid lowering agents, anticoagulants and mild immunosuppressants. Their disease modifying activity is known but the true mechanisms are not very clear. This class of drugs is particularly useful in the antiphospholipid syndrome. The only adverse effect of these agents is retinal pigmentation and corneal anesthesia.

Corticosteroid therapy[161] (Table 10) is reserved for patients with organ compromise and evidence of serological activity like elevated antinative DNA antibodies, low total hemolytic complement, or low C3 and C4.[162] The dose of such agents will vary with the extent of disease. In some cases, it is preferable to use parenteral pulse steroid therapy with large doses for

Table 9

Indications for Use of Nonsteroidal Agents in Lupus

Fatigue
Fever
Arthralgia/arthritis
Myalgias
Pleuritis/pericarditis

short periods.[161] The long-term use of these drugs can be associated with osteoporosis, easy bruising, and avascular necrosis of bone.

The physician should be familiar with the use of chemotherapeutic agents like methotrexate, cyclophosphamide (Table 11), and azathioprine (Table 12). These agents are used for life threatening organ involvement such as diffuse proliferative glomerulonephritis or lupus cerebritis. These agents have long-standing effects that vary with the duration of therapy and the dose used. These include a potent carcinogenic effect. There are also many new experimental agents.[163]

Use of drugs like the TNF inhibitors or those agents known to inhibit TH1 cytokines is not appropriate.

Rituximab is a monoclonal antibody that targets CD20, an antigen on B-cells. This drug has been used in refractory cases of lupus nephritis and neurological impairment.

Cyclosporine is used in SLE renal disease non-responsive to cytoxan or Imuran®, or active SLE refractory to other treatments. Patients respond to doses <5 mg/Kg/day.[164-166]

Thalidomide has great potential in the therapy of systemic discoid and subacute lupus. At doses between 50-100 mg/day, the role of clinical response is high. Peripheral neuropathy and amenorrhea are bad side effects.[167,168]

Human IVIG (either 30 grams/day x 4 days every three weeks to 400 mg/Kg/day x 5 days each month) are useful in the treatment of fever, arthritis and thrombocytopenia.[169]

Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase. This drug blocks both T- and B-cell proliferation because these cells depend on de-novo guanine synthesis. Ginzler et al showed this drug to be an effective treatment for lupus nephritis (superior to IV cytoxan).[170-172]

Table 10

Indications for Use of Glucocorticoid

Non-Major Organ Disease
Fever
Rashes: a) vasculitis rashes b) acute/subacute cutaneous lupus c) lupus panniculitis
Arthritis
Myositis
Lymphadenopathy
Pleuritis/pericarditis, moderate to severe
Major Organ Disease
Proliferative or membranous glomerulonephritis
Interstitial lung disease/pulmonary fibrosis
Myocarditis
Central and peripheral nervous system disease
Autoimmune hemolytic anemia
Autoimmune thrombocytopenic purpura
Systemic necrotizing vasculitis

Table 11

Indications for Cyclophosphamide Therapy in Lupus

Kidney
Diffuse proliferative glomerulonephritis
Membranoproliferative glomerulonephritis
Lung
Pulmonary hemorrhage
Interstitial lung disease
Pulmonary hypertension (?)
Nervous System
Cerebral or cerebellar disease
Peripheral neuropathy
Hematological Disease
Aplastic anemia
Autoimmune hemolytic anemia
ITP
Systemic necrotizing vasculitis

Table 12

Indications for the Use of Azathioprine in Lupus

Major organ disease or disease resistant to glucocorticoid or recurrent during glucocorticoid tapering
Intolerable glucocorticoid toxicity
Membranous glomerulonephritis (some patients)
Diffuse proliferative glomerulonephritis with mild to moderate renal scarring (some patients)
Antimalarial-resistant discoid lupus
Vasculitis rashes resistant to glucocorticoid

2. Antiphospholipid Syndrome (APLS)

Introduction

The antiphospholipid syndrome is an unusual disease characterized by the presence of recurrent abortions, thrombocytopenia, and arterial and venous thromboses.[25,173,174] Specific antibody tests are positive and might include the presence of a lupus anticoagulant and antibodies to negatively charged phospholipid like cardiolipin. The disorder can occur by itself as the primary form or with other diseases like lupus or Sjögren's syndrome. The clinical or laboratory features do not vary when the patient has a secondary or primary form of the disease.[175] Recently, the criteria for the diagnoses of this disease became available and they have been refined at the 9th International Workshop.[176]

Epidemiology

This illness can occur in children or adults. Finding the disease in young females is common because of the fetal wastage aspects of the disease. The disease occurs in families and some families have associated abnormalities like factor S deficiency or the presence of factor V Leiden.[177] There are also reports of this syndrome occurring with the C4 null haplotype. Polymorphisms of class II antigens in this syndrome are of interest, but a direct association with the disease does not exist.[178] Another major issue with regard to this syndrome is premature atherosclerosis. Early atherosclerosis is common to lupus and the antiphospholipid antibodies are proatherogenic and the subject of vigorous study.[179]

Etiopathogenesis

Not all patients with this syndrome experience symptoms and signs. The reasons for the thrombotic nature of certain individuals are under study. Mouse studies have shown that the antiphospholipid antibodies have thrombogenic potential, are toxic to the developing placenta of developing fetuses, and can be produced when immunodysregulation is achieved.[149] Indeed, the antiphospholipid syndrome can be induced by HIV infection.[180] Certain medications such as procainamide and minocycline can produce antibodies and thromboses by unknown mechanisms.[181]

As mentioned, the mechanism of thrombosis induction remains unknown, although there are many theo-

ries. One thing is clear: A prothrombotic state is induced in patients that clot and have abnormal antibody tests. These antibodies bind to the phospholipid of clotting factors and bind to the platelet surface in selected instances, causing the thrombocytopenia involved in the syndrome. Some hypotheses include enhancement of thromboxane synthesis, inhibition of prostacyclin synthesis, stimulation of tissue factor production by endothelial cells, protein C activation, neutralization of factor Va inactivation, factor X activation, and the direct binding of cofactors like prothrombin and beta 2 glycoprotein.[182] The latter two antigens are accepted as the primary targets of the phospholipid antibody.[183] Beta 2 glycoprotein or apolipoprotein H is of considerable interest since it is one cofactor to the phospholipid molecules; namely, it binds negatively charged phospholipid molecules.[184] The beta 2 glycoprotein molecules are natural anticoagulants. Since the discovery of this cofactor, several other cofactors have been described which bind to negatively charged phospholipid and become the targets for autoantibody. Recent experiments show that injection of beta 2 glycoprotein into mice results in antibodies to both the beta 2 glycoprotein and phospholipid.[185] In essence, the clotting process involves the antibodies that interact with antigens on the endothelial surface. Beta 2 glycoprotein I facilitates this interaction. Endothelial cells are then stimulated to produce adhesion molecules that bind monocytes. Platelet binding occurs and there is disruption of the adhesion shield. Specifically, Annexin V is affected, leading to progression of the clot.

Table 13

Classification Criteria for the Antiphospholipid Syndrome

Clinical
1. Vascular thrombosis: venous, arterial, or small vessel
2. Pregnancy morbidity: 3 or more consecutive abortions (<10 wks) 1 or more fetal deaths (>10 wks) 1 or more premature births (<34 wks) because of severe preeclampsia or placental insufficiency
Laboratory
1. Anticardiolipin antibody: IgG and/or IgM (medium/high titer)
2. Lupus anticoagulant On two or more occasions, 6 weeks or more apart

Adapted from Wilson W, et al. Arthritis and Rheumatism, *1999.*

Clinical Presentation

The presentation of these patients can be varied. Blood vessels of all sizes can be thrombosed in patients with this disease. These thromboses are unrelated to antibody levels. While deep vein thrombosis is the most common presenting complaint among young females with the disease, a patient can present for the first time with pulmonary embolus, renal artery thrombosis, cerebral infarction, retinal vein occlusion, or even middle ear infarction. Spontaneous occlusion of the hepatic veins (Budd-Chiari syndrome), the thalamic arteries of the brain, and the saggital sinus of the skull have been observed in isolated fashion in some patients. Patients who experience sudden infarction of multiple sites are said to have the "catastrophic phospholipid syndrome."[186] Various hepatic conditions like hepatic artery thrombosis are found in this syndrome. Autoimmune hepatitis is also associated with APLS.[187]

Low platelet counts and elevated partial thromboplastin times are characteristic of these patients.[188] The platelet antigens may be selected targets for these antibodies. Such patients usually do not bleed unless the platelet counts go below 30,000. Use of nonsteroidal anti-inflammatory agents and aspirin in these patients should be avoided, although the new cyclooxygenase 2 inhibitors are used by some physicians since both bleeding times and clotting functions are not affected.[189] As with all of the autoimmune diseases, other more perplexing symptoms may complicate the presentation of these patients. These include migraine headaches,[190] livedo reticularis, leg ulcers, a variety of cardiac murmurs caused by Libman-Sacks vegetation, chorea, and transverse myelitis.[25] Myocardial infarction can also occur in normal coronaries in those with the antiphospholipid syndrome.[103,191] Optic scleri-

tis or blindness in one or both eyes due to retinal vein infarction can also occur.[192] The antiphospholipid antibodies can attack the adrenal gland and cause severe adrenal insufficiency.[193]

Recurrent miscarriages are also common in patients who have these antibodies.[149] This loss can occur at any stage of the pregnancy. Recurrent fetal loss can be associated with antibodies to factor XII and other factor specific antibodies.[194] The cause of the fetal death is suspected to be placental vessel thrombosis; however, the antibodies are toxic directly to the placenta from mouse studies, and it is possible that they are trophotoxic themselves.[195] Pregnancy loss remains a criterion for this disease and can occur at any time during the gestation. Fetal death in the second or third trimester is characteristic. The aborted fetus is usually anatomically normal except "small for dates." The risk for thrombosis in mothers with antiphospholipid syndrome is higher during pregnancy. Low molecular weight heparin has been used to decrease the risk of thrombotic occurrences during pregnancy.[196]

The difficulty with this syndrome is the large differential diagnosis that must be considered before institution of things like lifelong anticoagulation. Consideration of other conditions like Factor V Leiden (activated protein C resistance), protein C, protein S and antithrombin III deficiency should be part of the workup. The list of other diseases to consider includes dysfibrinogenemia, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, polycythemia vera, and the side effects of oral contraceptives. Many other conditions that are too numerous to list involve the clotting mechanism. There are also varieties of physical conditions that are associated with arterial thrombosis. Phospholipid syndrome only accounts for a small portion of the causes of early fetal demise. Conditions that involve chromosomal abnormalities, anatomic abnormalities of the female reproductive tract, and endocrine, infectious, autoimmune and drug-induced disorders of the mother must be taken into account. Infertility can be associated with a variety of ailments and its presence does not mandate an expensive immunological work-up or the institution of immunosuppressive drugs.[197]

Laboratory Diagnosis

The tests best known for the diagnosis of this disease are the cardiolipin antibodies and the lupus anticoagulant. However, a much simpler assay, which must be performed before those tests, is the prothrombin time (PT) and the activated partial thromboplastin time (PTT). If the antiphospholipid syndrome is present, the PTT is usually elevated, sometimes very little. Rarely are there antibodies without this screening abnormality. Once a suspicion has been raised, one must measure antibodies against negatively charged phospholipid, which includes cardiolipin as the most widely available. The three isotypes—IgM, IgG and IgA—can be measured, although IgG and IgM are most commonly positive. Units of positivity are expressed in GPL, MPL or APL units. Quantitation is important, although the titer of the antibody does not correlate with the propensity for clotting. The lupus anticoagulant—a misnomer, of course, since it is associated with clotting—is identified by certain criteria: first is the prolonged PTT, Russell viper venom or kaolin clotting time; second is the mix test wherein the patient's plasma is mixed with normal plasma which corrects the abnormal PTT; and last is the normalization of the test by the addition of platelets or phospholipid to the patient sera.[198,199]

The measurement of cofactor antibodies is popular in some hospitals, specifically against β2 glycoprotein I. It is possible to obtain isotypes and titers of this antibody. However, the predictable value of this antibody is not clear. It is true that this antibody often is positive when the other phospholipid titers are not, suggesting that there is a role for this test in the diagnosis of the disease. Data, however, are forthcoming and not yet convincing.

Therapy

The therapy of the phospholipid syndrome is controversial. There are often questions about when to treat the patient, and the nature of the medications, such as whether anticoagulants or immunosuppressive drugs should be used.

There are a variety of recommendations that could be made with regard to the treatment of APLS. First is prophylactic anticoagulation, which is certainly not justified in patients without a history of thrombosis. If

there is a history of thrombosis such as DVT or pulmonary embolism, long-term anticoagulation is appropriate with an international normalized ratio (INR) of 3 to 3.5. Therefore the treatment of this condition is divided into treatment as prophylaxis and after thrombosis.

Prophylaxis

A regular dose of aspirin (325 mg/d) did not demonstrate any protection against DVT and pulmonary patients with cardiolipin antibodies.[200] In women with pregnancy loss who have these antibodies such prophylaxis with aspirin might actually be of benefit.[201] Hydroxychloroquine is a useful agent for the treatment of lupus and may actually be of benefit as a prophylactic agent for patients with antiphospholipid antibodies.[202,203]

After Thrombosis

The treatment after thrombosis should be the same as one would use for any other procoagulant condition. A problem exists with the use of heparin in these patients, namely that the PTT is usually elevated and cannot be monitored except with the use of a specific heparin assay or the activated clotting time. One must use an assay that is insensitive to antiphospholipid antibodies. The use of heparin in the acute setting would predate the eventual use of warfarin. The lifetime use of warfarin therapy is highly recommended in these patients because the presence of elevated cardiolipin antibodies 6 months after an episode of venous thromboembolism is a predictor for disease occurrence and death.[204] In one retrospective study, antibodies and a past history of thrombosis showed that treatment with warfarin that was high enough to produce an INR of 3-3.5 was significantly more effective in preventing further thrombotic events. Some clinicians argue that the presence of arterial emboli themselves require a more intense treatment with high doses of warfarin, but the data are lacking.[205]

Pregnancy

In the pregnant patient, heparin remains the drug of choice without immunosuppression. The use of low molecular weight heparin and low-dose aspirin is the regimen of choice for such patients although the added effects of low-dose aspirin are questionable. Low-dose heparin must be adjusted throughout the pregnancy because of weight change. The discovery of antiphospholipid antibodies during pregnancy in the absence of a history of fetal loss or thrombosis does not warrant any prophylaxis.[40,41,42,206] Some have advocated the use of warfarin after fetal organogenesis is complete; however, there is an increased risk of bleeding for the fetus.[207]

Catastrophic Antiphospholipid Syndrome

The use of anticoagulation alone in this variant of APLS may not be enough. There are data to support the use of steroids, cyclophosphamide, intravenous gamma globulin, and plasmapheresis in addition to anticoagulation. This may be the only indication for immunosuppression in this syndrome.[186]

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