Systemic Lupus Erythematosus

The Clinical Picture

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Synonyms

Lupus erythematodes, disseminated lupus erythematosus, lupus superficialis.

Definition

Systemic lupus erythematosus is a chronic inflammatory collagenosis (connective tissue disease) affecting primarily women and girls. The illness is characterized by recidivistic fever episodes with exanthem and skin erythema and can affect all joints and organs.

Etiology

Presumably, systemic lupus erythematosus (SLE) is an autoimmune reaction. The presence of antinuclear antibodies (ANA) and antibodies against DNA support this assumption. Immune complexes circulate in the blood and accumulate in the vessel walls, leading not only to necrotic and thrombotic inflammation of the vessels (immune complex vasculitis) with accumulation of fibrinoid in small arteries and arterioles but also to lupus nephritis. Cell-mediated immunity and suppressor T-cells are reduced. In addition, combinations of selective IgA deficiency and heterozygous C2 deficiency are seen.

The condition is thought to be genetically determined. SLE is familial in 10% of cases and can also affect homozygous twins. An immunogenetic predisposition is indicated by the presence of the lymphocyte antigen HLA-B8, the B-cell antigen HLA-DR3 and the complement system C4a. Viral infections and environmental factors (sunlight) also play a role in triggering SLE.

Nothing is known about the incidence of the disease; prevalence is around 0.03%. SLE can develop at any age but most frequently affects women in their thirties, forties, and fifties. In 20% of patients the illness begins in childhood, but not before age five and usually after age eight. Girls are affected eight times as often as boys; in prepuberty the proportion is 3:1. All races are susceptible, but dark-skinned races are affected more often than light-skinned.

The following categories of lupus are recognized:

- systemic lupus erythematosus (SLE)
- subacute cutaneous lupus erythematosus (SCLE)
- chronic discoid lupus erythematosus (CDLE)

Symptoms	Frequency in % initially	Frequency in % over the course of the illness
• Malaise, weight loss, growth retardation	96	100
• Changes in skin and mucous membranes:		
Butterfly rash	51	56
Dermatitis	69	76
Photosensitivity	16	16
Alopecia	16	20
• Hematologic changes:		
Anemia	43	47
Leukopenia	60	71
Thrombocytopenia	22	24
Positive LE cell finding	86	100
• Fever	84	100
• Nephritis	84	86
• Muscular and skeletal symptoms:		
Arthritis	72	76
• Pleural and pulmonary diseases:		
Pleuritis	31	36
• Hepatosplenomegaly:		
Hepatomegaly	43	47
Splenomegaly	20	20
• Neurological disorders	9	31
• Cardiac complications:		
Pericarditis	40	47
• Hypertension	10	28
• Eye involvement (retinal vasculitis)		31
• Gastrointestinal symptoms (pancreatitis)		27
• Raynaud's phenomenon	16	24

Tab. 1: Manifestations of lupus erythematosus in children [4,6]

- neonatal lupus erythematosus (NLE)
- anticardiolipin syndrome
- medication-induced lupus erythematosus
- pseudo-lupus syndrome

SLE in Children

Systemic lupus erythematosus can either take an acute form, progressing rapidly and affecting multiple organ systems, or run its course as a chronic recurrent illness with long symptom-free intervals. The illness is diagnosed within six months in approximately three fourths of all patients, but occasionally four or five years can go by before a diagnosis is made. Table 1 lists the frequency of symptoms in children by percent, with separate columns for initial symptoms and those occurring in the further course of the illness.

The most frequent initial symptoms are skin changes and general malaise. Because of its shape, the facial erythema that develops across the zygomatic arch is known as "butterfly rash." In addition, a maculopapular scaly rash can be observed on the face. It eventually spreads to the neck and upper thorax and finally to the hands, and after a number of years affected areas of skin may atrophy. Alopecia may develop, and photosensitization also occurs frequently. Painless lesions of the oral mucosa often develop. Fever is not universally present in the initial stages. With regard to kidney involvement (lupus nephritis) the course of the illness is either benign or progressive, and only a kidney biopsy can predict the patient's chances with any clarity (Table 2).

Autoantibodies against:	Frequency	Clinical findings
double-strand DNA	80%	kidney involvement
single-strand DNA	90%	
SS-A	50%	kidney,lung, or skin involvement
SS-B	15%	
smooth musculature	35%	isolated CNS disorders
histone	40%	medication-induced SLE
cardiolipin	50%	predisposition to thrombosis
erythrocytes	10-50%	anemia
thrombocytes	<10%	thrombocytopenia
lymphocytes	>50%	lymphopenia

Tab. 3: Specific laboratory results in SLE [2]; SS-A, SS-B = nuclear antigens A and B, associated with Sjögren's syndrome

SLE in Adults

Arthralgia appears in 90% of adult patients. Enlargement of the liver and spleen is also observed in over 50% of adult cases, while painfully enlarged lymph nodes are especially prevalent among children and adolescents. Recurrent pleuritis and pericarditis have been described as complications. Pulmonary hypertension may develop, while symptoms involving the eyes and the gastrointestinal tract are less common, as are peripheral circulatory disturbances (Raynaud's phenomenon).

The following categorization of adult systemic lupus erythematosus has been suggested by the American College of Rheumatology and the American Rheumatism Association:

- butterfly rash on the cheeks
- macular skin rash on the face and neck (cutaneous LE)
- photosensitivity (increase in symptoms from exposure to sunlight)
- oral and/or nasopharyngeal ulceration (usually painless)
- non-deforming polyarthritis with arthralgia and joint effusions (two or more joints affected)
- serositis (painful pleuritis, pericarditis, Libman-Sacks endocarditis)
- CNS involvement with neurological disorders (seizures, psychosis, pseudotumor cerebri)
- typical laboratory findings (see Table 3)

Immunoserology and Hematology

Abnormal titers of antinuclear antibodies (ANA) have been found, as have antibodies against DNA, smooth muscle (Sm), cardiolipin, phospholipids, erythrocytes, leukocytes, and thrombocytes. These antibodies cause hemolytic anemia with low hemoglobin, leukopenia (>4,000/µl), lymphopenia (>1,500/µl) and thrombocytopenia (>100,000/µl). The leukocytes do not respond to infections and remain low even in bacteremia.

A direct Coombs test, which is used to detect hemolytic anemia, may be positive. Similarly, rheumatoid factors test positive in 30% of cases. Cold agglutinins are occasionally present. During acute phases of the illness, concentrations of C4 serum complement typically decrease, while the C3 complement usually remains normal.

The LE cell phenomenon (rosette formation from phagocytized nuclear mate-

Histology		Remissions	Kidney failure	Fatalities due to uremia
Type I	normal	-	-	
Type II	mesangial form	+	-	-
Type III	focally proliferative form	++	+	+
Type IV	diffusely proliferative form	+	++	+++
Type V	membranous form	+	++	+
Extraglomular lesions		+	++	++

Tab. 2: WHO categorization of lupus nephritis [4]

rial in a large vacuole) was discovered as early as 1948 by Hargraves et al [5] and is not as good a predictor as the specific antibodies, since it is only reliably positive in early or acute phases of the illness. A chronic false-positive serologic test for syphilis (VDRL) indicates a predisposition to recurrent thrombosis.

In lupus nephritis, proteinuria (<0.5 g/day), erythrocyturia, and leukocyturia are present. The significant increase in ESR that results from hypergammaglobulinemia is not highly specific for this condition.

Differential Diagnosis

Lupus erythematosus must be distinguished from juvenile rheumatoid arthritis, acute glomerulonephritis caused by other factors, hemolytic anemia, leukemia, mononucleosis, acute rheumatic fever accompanied by carditis, septicemia, and allergic or contact dermatitis.

Neonatal lupus erythematosus (NLE) represents a special form of the disease. It occurs when the mother suffers from active SLE during pregnancy and her IgG antinuclear antibodies are transmitted transplacentally. The infant develops a butterfly rash or discoid lupus skin changes. Laboratory tests detect thrombocytopenia, leukopenia, and mild hemolytic anemia. Congenital heart disease with AV block or endocardial fibroelastosis may also be present.

Approximately 3-12% of lupus cases are induced by medications such as hydralazine, hydantoin, oxazolidine, procainamide, and sulfonamides, and symptoms may disappear spontaneously once the medication is discontinued. In these patients both antinuclear and antihistone antibodies are present, but there is no evidence of anti-DNA antibodies.

In *pseudo-lupus syndrome* kidney and CNS involvement are absent, but the skin changes are the same as in true SLE. Antimitochondrial antibodies are present but antinuclear factors are not.

Therapy

Conventional therapy varies, depending on the severity of the illness.

Mild episodes (fever, arthritis, pleuritis, pericarditis, headaches, skin rash): nonsteroidal anti-inflammatories such as acetylsalicylic acid; antimalarials such as hydrochloroquine, chloroquine, and quinacrine.

Severe episodes (with hemolytic anemia, thrombocytopenic purpura, massive pleural and pericardial effusions, kidney involvement, vasculitis in the extremities, or CNS involvement): corticoids and immunosuppressants such as azathioprine and cyclophosphamide.

Episodes with CNS involvement: methylprednisolone, perhaps in combination with cyclophosphamide and plasmapheresis.

In addition, antibiotics are indicated for infections, while patients with phospholipid antibodies may require coagulants.

General therapeutic measures include dietary changes and avoiding sunlight.

Biological therapy emphasizes strengthening the body's own defenses. Homeopathic remedies that come into question include acidum benzoicum, acidum formicicum, cactus grandifloris, causticum, colchicum, bryonia, dulcamara, kalmia, mercurius, nux vomica, rhododendron, and thuja occidentalis. In phytotherapy, stinging nettle, echinacea, dandelion, devil's claw, and red clover may be used.

Prognosis

The prognosis depends on the symptoms, the course of the illness, and the extent to which the disease is localized. If the acute phase is brought under control therapeutically, long-term prognosis improves: in such cases the ten-year survival rate is over 95%.

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