# STUDY OF SOME OPPORTUNISTIC PARASITIC INFECTIONS IN EGYPTIAN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

THESIS
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By
Dr. MAZLOUM MAHMOUD AHMED
PARASITOLOGY DEPARTMENT
FACULTY OF MEDICINE AIN SHAMS UNIVERSITY

SUPERVISORS

Prof. Dr. MOHAMED FATHY TAMARA

Professor of General Medicine & Head of Rheumatology unit ,
Faculty of Medicine Ain-Shams University



Prof. Dr. MAGDA EL-SAYED AZAB
Professor of Parasitology
Faculty of Medicine Ain-Shams University

Prof. Dr. EMAD AHMED EZZAT BARAKAT
Professor of General Medicine, Rheumatology Unit
Faculty of Medicine Ain-Shams University

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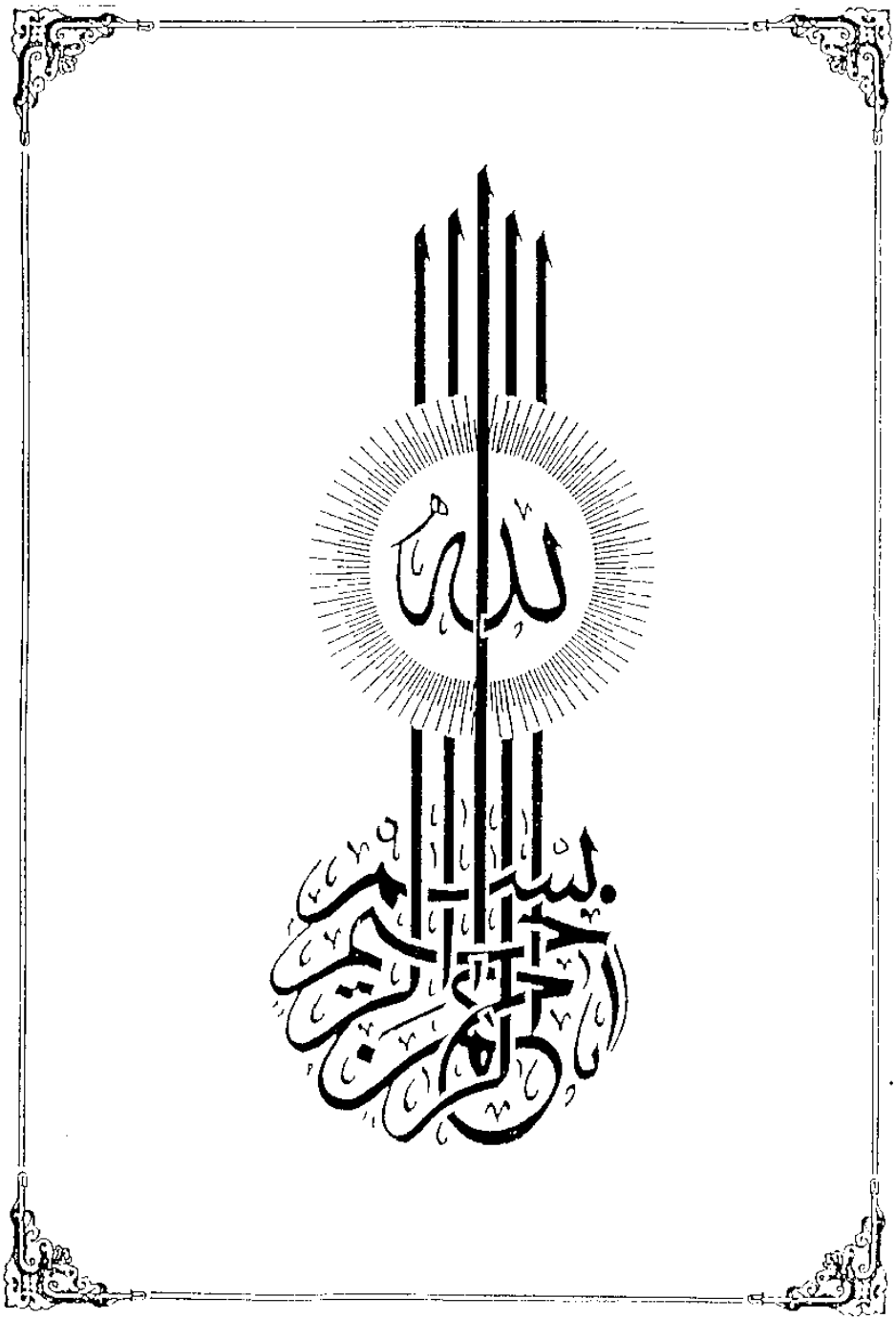

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CONTENTS

# LIST OF ABBREVIATIONS

ANAs = antinuclear antibodies
*Crypt.* sp. = *Cryptosporidium* species
*E. histolytica* = *Entamoeba histolytica*
*G.lamblia* = *Giardia lamblia*
Ig = immunoglobulin
IFAT = indirect fluorescent antibody test
SLE = systemic lupus erythematosus
*St. stercoralis* = *Strongyloides stercoralis*
*T. gondii* = *Toxoplasma gondii*
*Tr. vaginalis* = *Trichomonas vaginalis*

# INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease of unknown cause that affects many organ systems and is characterized by the presence of multiple antibodies that participate in immunologically mediated tissue injury ***(Rothfield, 1993)***. The most important finding in SLE is an imbalance between the humoral and cellular components of the immune response. Coinciding with B-cell hyperactivity, there is T-cell hypoactivity. For this reason, SLE was once considered to be a " B-cell " disease. T cells , however, have a primary role in the initiation of SLE and other auto immune diseases ***(Wofsy and Seaman, 1987)***. So, patients with SLE are considered to be immunocompromised and liable to infections with opportunistic organisms including parasitic ones.

The opportunistic infections should be anticipated as a distinct possibility in every patient with a known derangement of host resistance. Anticipation simply means , a careful periodic laboratory evaluation of paients at risk , before infection has become clinically evident ***( Geddes and Ellis , 1985 ).***

The recorded opportunistic parasites are :*Toxoplasma gondii* (*T. gondii*),*Cryptosporidium* species (*Crypt.* sp.),*Giardia lamblia* (*G. lamblia*) and *Strogyloides stercoralis* (*St. stercoralis*) ( Faussett et. al., 1993). ***Wilcox et. al. ( 1990 )*** compared the *Toxoplasma* serological status of patients with SLE with that of healthy controls ; high titers of *Toxoplasma* antibody were significantly more common in patients with SLE .

Although , the presence of certain immune abnormalities seems to render the human host more susceptible to giardiasis , symptomatic giardiasis does not appear to be a major problem in patients with AIDS ***(Stevens and Gillen 1990 )***.Cryptosporidial infection in patients with AIDS or other types of immunocompromise often begin insidiously and escalates in severity as the immune defect becomes more pronounced ***(Soave, 1990)***. Disseminated strongyloidiasis has been seen increasingly in patients with defective cell mediated immunity, who are immunosuppressed either as a result of disease, because of the administration of immunosuppressive agents or both ***(Siegman et. al. 1981).***

# *REVIEW OF LITERATURE*

# SYSTEMIC LUPUS ERYTHEMATOSUS

## DEFINITION:

SLE is a disease of unknown cause that affects many organ systems and is characterized by the presence of multiple autoantibodies that participate in immunologically mediated tissue injury ***(Rothfield, 1993)***.

## PREVALENCE AND INCIDENCE :

SLE affects individuals of all races, but its prevalence varies in different countries. It has ranged from approximately 0.13 ***(Hochberg, 1990)*** to 0.51 cases ***(Fessel, 1988)*** per 1000 population in studies from the United States and Europe respectively. The mean age at diagnosis is 30 years and 90% of patients at such age are usually females ***(Jonsson et. al., 1990).*** Incidence rates of SLE in the United States range from 1.8 to 7.6 cases per 100000 persons per year ***(Hochberg, 1990)***.

## AETIOLOGY AND PATHOGENESIS:

The aetiology of SLE is unknown. The immune hyperactivity that characterizes SLE appears to drive from abnormal immune activation and loss of self tolerance that could provide the genetic basis of the disease. An inherited defect in immune regulation, as complement and other deficiencies, may underlie the disorder in many individuals.The signs and symptoms are thought to be caused by the autoantibodies that react with self constituents, in the presence of complement system, and initiate inflammatory responses and tissue damage by deposition of antigen-antibody complexes ***(Wilson et. al. 1989).*** Environmental agents that trigger disease include foods, drugs, ultraviolet light and micro-organisms as viruses, bacteria and parasites. So, environmental, metabolic, and hormonal factors appear to act on the genetically conditioned immune substratum to predispose to or protect against disease expression ***(Steinberg, 1992).***

## IMMUNOLOGICAL ASPECTS OF SLE :

The most consistent finding in SLE is an imbalance between humoral and cellular components of the immune response with B-cell hyperactivity associated with T-cell hypoactivity ***(Horwitz, 1993).*** In patients with SLE, there is spontaneous B-cell proliferation and immunoglobulin secretion is increased in patients with either active or inactive disease ***(Dar et al, 1988)***. Moreover, non affected family members of SLE patients have an increased numbers of Ig-secreting cells ***(DeHoratius and Levinson, 1981)***. Autoantibodies in SLE can be divided into 2 classes as mentioned by ***Tan (1993)***. The first includes autoantibodies to nuclear and cytoplasmic antigens that are not tissue specific but react with antigens present in many tissues and organs. Those of great clinical significance are antinuclear antibodies (ANAs), which can be divided into 4 main groups: those directed against double strand DNA, single-strand DNA, histones and non histone nuclear proteins. A second class of autoantibodies includes those that are tissue specific, that is, those directed against cellular elements in the heomopoetic system, such as red cells, white cells, and platelets, and antibodies to tissue specific antigens (thyroid, liver, muscle, stomach, and adrenal glands).

The most important immune mediators in SLE are Interleukin(IL) 1, IL 2 and immune interferon (IFN-y) ***(Byron and Hughes, 1988)***. IFN-y regulates the expression of major histocompatibility complex (MHC) products on immune cells, inhibits lymphocyte proliferation, and has mixed effects on antibody production ***(Oppenheim, et. al., 1991)***.
Abnormalities in T-cell subsets, functional properties of T cells and cytokine production are chiefly observed in patients with active disease.
Because of abnormalities of CD4-+ve cells, these cells are unable to provide the necessary help for CD8-+ve cells to down regulate antibody production. Under these conditions, both CD8 + ve T cells and natural killer (NK) cells support instead of suppress antibody production in SLE ***(ISraeli et. al., 1990).***

## CLINICAL MANIFESTATIONS:

SLE is a disease characterized by exacerbations and remissions, and is highly variable in onset and course. At onset, SLE may involve only one organ system (with additional manifestations occurring later) or may be multisystemic. The incidence of clinical manifestations are listed in table 1 ***(Hahn, 1988).***

**Table 1. Clinical manifestations of SLE**

| | % of patients during course of SLE |
|---|---|
| Systemic | 95 |
| Fatigue, malaise, fever, anorexia, nausea, weight loss | |
| Muscloskeletal | 95 |
| Arthralgias/ myalgias | 95 |
| Nonerosive polyarthritis * | 60 |
| Hand deformities | 10 |
| Myopathy/ myositis | 40/5 |
| Ischemic necrosis of bone | 15 |
| cutaneous | 80 |
| Malar rash * | 50 |
| Discoid rash * | 15 |
| Photosensitivity* | 40 |
| Oral ulcers* | 40 |
| Other rashes-maculopapular, urticarial, bollous, subacute cutaneous lupus | 40 |
| Alopecia | 40 |
| Vasculitis | 20 |
| Panniculitis | 5 |
| Haematologic | 85 |
| Anemia (of chronic disease) ] | 70 |
| Hemolytic anemia ] | 10 |
| Leukopenia(< 4000/mm3) ] * | 65 |
| Lymphopenia(< 1500/mm3 ] | 50 |
| Thrompocytopenia(<100000/mm3] | 15 |
| Circulating anticoagulant | 10-20 |
| Splenomegaly | 15 |
| Lymphadenopathy | 20 |
| Neurologic | 60 |
| Organic brain syndromes | 35 |
| Psychosis } | 10 |
| Seizures ] * | 20 |

**Table 1. Clinical manifestations of SLE (cont.)**

| | | % of patients during course of SLE |
|---|---|---|
| Other CNS (see text) | | 15 |
| Peripheral neuropathy | | 15 |
| Cardiopulmonary | | 60 |
| Pleurisy | ] | 50 |
| Pericarditis | ] * | 30 |
| myocarditis | ] | 10 |
| Endocarditis (Libman-Sachs) | | 10 |
| Pleural effusions | | 30 |
| Lupus pneumonitis | | 10 |
| Interstitial fibrosis | | 5 |
| Pulmonary hypertension | | <5 |
| ARDS/hemorrhage | | <5 |
| Renal | | 50 |
| Proteinuria >500 mg/24 h | ] | 50 |
| Cellular casts | ] | 50 |
| Nephrotic syndrome | ] * | 25 |
| Renal failure | ] | 5-10 |
| Gastrointestinal | | 45 |
| Nonspecific ( anorexia, nausea, mild pain, diarrhea | | 30 |
| Vasculitis with bleeding or perforation | | 5 |
| Ascitis | | <5 |
| Abnormal liver enzymes | | 40 |
| Thrombosis | | 15 |
| Venous | | 10 |
| Arterial | | 5 |
| Foetal loss | | 30 of (pregnancies) |
| Ocular | | 15 |
| Retinal vasculitis | | 5 |
| Conjunctivitis/episcleritis | | 10 |
| Sicca syndrome | | 15 |

*** In addition to two positive laboratory tests [ positive ANA plus one or more of (1)positive LE cells, (2) anti-dsDNA, (3) anti-sm, or (4) false positive VDRL]. a combination of these clinical and laboratory manifestations totaling four meet American Rheumatism Association criteria for classifying patients as SLE. Stracketed features count as one , even if more than one is present, e.g. leucopenia plus thrombocytopenia = one criterion. Quoted from *Hahn, 1988*. p. 1434.**

Arthralgias are the single most common manifestation in SLE ***(Steinberg, 1992)***. Pain is often out of proportion to physical findings seen usually in joints of hands, wrists and knees . Also, mild mental dysfunction is the frequent neurologic manifestation. Standard laboratory measures of disease activity (Table, 2) often do not correlate with neurologic manifestations ***(Hahn, 1988).***

Non specific gastrointestinal symptoms are common, but vasculitis of the intestine is the most dangerous manifestation. It causes acute or subacute cramp pain, vomiting and diarrhea and can lead to intestinal perforation and death. Patients generally respond to glucocorticoid therapy. Acute pancreatitis occurs and can be severe; it may result from active SLE or from corticosteroid therapy. Elevated serum levels of liver enzymes, especially transaminases, are common in patients with active SLE but are not associated with significant hepatic damage; they return to normal as the disease is treated ***(Hahn, 1988).*** Hepatomegaly occurs in about 30% of patients, more commonly among children than among adults-onset patients. Also, slight to moderate splenomegaly, not usually associated with hemolytic anaemia, is present in 20% of patients and is more common in children ***(Rothfield, 1993).***

Lymph nodes enlargement occurs in about half of SLE patients with active disease. Lymphadenopathy is more common in children than in adults ***(Rothfield, 1993)***. Adenopathy is usually generalized but may be limited, and the enlarged nodes are usually non tender. Microscopic changes in lymph nodes are non specific, and differ from that of *Toxoplasma* which are specific changes. SLE changes consist of follicular hyperplasia, which may be associated with areas of necrosis resembling giant follicular lymphoma ***(Rothfield, 1993).***

The most important ocular manifestation of SLE is retinal vasculitis with infarcts; blindness can develop over a period of days and may be the first symptom of the disease ***(Rothfield, 1993)***

One or more haematologic abnormalities are present in nearly all SLE patients with active disease . Most common is a mild to moderate normocytic normochromic anaemia caused by retarded erythropoiesis.

Leukopenia is common and usually reflects lymphopenia which is usually persistent during periods of disease activity .In general, it is not associated with recurrent infections and does not require treatment. Leukocytosis resulting from corticosteroid therapy also occurs in SLE patients ***(Rothfield, 1993).***

**Table 2. Laboratory manifestations of SLE**

| **Tests that help confirm the clinical diagnosis and predict severity** | **Tests that may be helpful in following the clinical course *** |
|---|---|
| Relatively specific for SLE | Titer of anti-dsDNA |
| anti-dsDNA | Serum complement levels, |
| anti-Sm | Westergren E.S.R. |
| Non specific: | Haematocrite |
| ANA ( most sensitive ) | Leukocyte count |
| THC, C3, C4 | Platelet count |
| Anti-Ro | Urinalysis |
| Direct Coombs test | Serum creatinine |
| VDRL | |
| PTT | |
| Anticardiolipin | |
| Haematocrite | |
| Leukocyte count | |
| Platelet count | |
| Urinalysis | |
| Serum creatinine | |

*** For each patient, the pattern of laboratory abnormalities (if any) associated with a disease flare should be established and only those tests used subsequently as adjuncts to clinical assessment. Quoted from *Hahn, 1988.* p. 1454.**

Since SLE is a disease of young women, pregnancy is a frequent occurrence. Fertility rates are normal in patients with SLE but the rate of spontaneous abortion and stillbirths is high (3o to 50%), especially in the untreated patients with active disease and lupus anticoagulant and/or antibodies to cardiolipin. Normal deliveries are the rules in the well controlled patients taking low doses of corticosteroids for at least 6 months prior to conception ***(Rothfield, 1993).***

## LABORATORY FINDINGS:

Antinuclear antibodies are the best screening test and is the most sensitive one. Antibodies to ds-DNA and to Sm are relatively specific for SLE; other autoantibodies are not. High serum levels of ANA and anti DNA and low levels of complement usually reflect disease activity, especially in patients with nephritis ***(Hahn, 1988)***. The E.S.R. is elevated in nearly all SLE patients and in most patients fall to normal when the disease becomes inactive ***(Rothfield, 1993)***. A diffuse elevation of serum y-globulin is observed in about 80% of patients with clinically active disease. Serum complement levels are usually depressed in active disease.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS:

SLE should be suspected in any person with a multisystem disease including joint pain. Diagnosis was made according to the Revised Criteria for SLE by the American Rheumatism Association (ARA) by ***Tan et. al. (1982)***. Manifestations included are indicated by asterisks in table 1. Although not included in the Revised Criteria, serum C3 levels are of major importance in the diagnosis of an individual with SLE.

The condition in children is frequently misdiagnosed as rheumatic fever or juvenile rheumatoid arthritis. The disease in adults is most commonly misdiagnosed as rheumatoid arthritis. Other diagnosis often applied to patients with SLE include Raynauds disease, haemolytic anemia, idiopathic or thrombotic thrombocytopenic purpurae, psychosis, vasculitis, progressive systemic sclerosis, lymphoma, autoimmune neutropenia, secondary syphilis, drug reaction, porphyria, multiple sclerosis, myasthenia gravis, polymyositis, glomerulonephritis, Henoch-Schonlein purpura, personality disorder, stroke, and seizure disorder ***(Steinberg, 1992).***
The possibility of drug-induced lupus should always be considered

## DRUG - INDUCED LUPUS:

Several drugs can cause a syndrome resembling SLE in individuals without any obvious predisposition to the disease. The most common offenders are procainamide, hydralazine, anticonvulsants (phenytoin, hydantoins, primidone), isoniazid, chlorpromazine, and oral contraceptives