Serum Complement 1q Antibody as a Predictive Marker for Lupus Nephritis and Lupus Activity

THESIS

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LIST OF ABBREVIATIONS

Ab	**Antibody**
ACR	**American Colleague Criteria**
Ag	**Antigen**
ALT	**Alanine aminotransferase**
ANA	**Anti nuclear antibody**
Anti-ds DNA	**Anti double stranded Deoxyneucleoprotein**
aPL	**Anti phoshpholipid**
AST	**Aspartate aminotransferase**
BILAG	**British Isles Lupus Assessment Group**
CBC	**Complete Blood Count**
CH50	**Total serum hemolytic complement**
C1INH	**Complement 1 inhibitor**
CNS	**Central Nervous System**
C1q	**Complement 1q**
CLR	**Collagen like region**
Cr	**Creatinine**
Cr.CL	**Creatinine clearance**
CRP	**C-Reactive protein**
CVS	**Cardiovascular System**
DNA	**Deoxyribonucleic acid**
DNP	**Deoxyribonucleic protein**
ECLAM	**European Community Lupus Activity Measure**
EBV	**Epstein Bar virus**
ELISA	**Enzyme Linked Immunosorbent Assay**
EM	**Electron microscopy**
ESR	**Erythrocyte sedimentation rate**
ESRD	**End stage renal disease**
FBS	**Fasting blood sugar**
FGF	**Fibroblast Growth Factor**
GFR	**Glomerular Filtration Rate**
GIT	**Gastro Intestinal Tract**
GN	**Glomerulonephritis**
HB	**Hemoglobin**
HLA	**Human Leucocyte Antigen**

HUVS	**Hypocomplementemic urticarial vasculitis**
IF	**Immunofluorescence**
Ig	**Immunoglobulin**
IL	**Interleukin**
ISN/RPS	**International Society of Nephrology/Renal Pathology Society**
Kg	**Kilogram**
LAI	**Lupus Activity Index**
LM	**Light microscopy**
LPS	**Lipopolysaccharaide**
MAC	**Membrane Attack Complex**
MBL	**Mannose Binding Lectin**
MPS	**Mononuclear phagocyte system**
NIH	**National Institutes of Health**
NSAIDs	**Non Steroidal Anti-inflammatory Drugs**
PAMPs	**Pathogen-associated molecular patterns**
PDGF	**Platelets Derived Growth Factor**
PLT	**Platelets**
RBCs	**Red Blood Cells**
S.Cr	**Serum creatinine**
SLAM	**Systemic Lupus Activity Measure**
SLE	**Systemic Lupus Erythematosus**
SLEDAI	**Systemic Lupus Erythematosus Disease Activity Index**
TNF	**Tumor Necrosis Factor**
USA	**United States of America**
VAS	**Visual analogue scale**
ITS	**World Health Organization**

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder in which the body's immune system incorrectly attacks the body's own tissues and organs. It may affect almost all organs in the body, with the kidney being most commonly involved. Renal involvement may be mild in some cases and very severe in other cases. **(Ringold et al., 2005).**

Lupus Nephritis occurs in approximately 50% of patients, sometimes it may be the first manifestation of SLE. Clinical features range from asymptomatic urinary abnormalities to full-blown nephritic syndrome or rapidly progressive renal failure**. (Gallelli et al, 2005).**

Several antibodies, especially those against double stranded DNA(anti-ds DNA),are believed to play a major role in the induction of glomerular inflammation.However,the lack of specificity of these biological markers for renal exacerbations has led to the search for other autoantibodies that might contribute to nephritis and help diagnose a renal flare.**(Marto et al, 2005).**

Autoantibodies to some complement proteins develop as a part of autoantibody response. **(Walport et al, 2002).**

Recently, anti-C1q autoantibodies have been proposed as a useful marker in systemic lupus erythematosus (SLE) since

their occurrence correlates with renal involvement and, possibly, with nephritic activity. **(Sinico et al., 2005)**.Also the presence of anti-c1q antibodies is associated with severe illness, including glomerulonephritis. **(Mark et al, 2002).**

Moroni et al 2001 reported that development or recurrence of nephritis was associated with rising titers of anti-C1q in the preceding six months and that these were more specific for active renal involvement than anti-dsDNA.So the monitoring of anti C1q Ab after the diagnosis of SLE might be helpful and represents a non-invasive biological marker in the follow-up of SLE patients. When the measurement shows no such Ab, the likelihood of severe lupus nephritis (stage III/IV) is low**. (Fremeaux et al, 2002).**

Aim of the Work

The aim of this work is to correlate the anti-C1q antibodies level in the sera of the patients with SLE, with the different markers of activity, renal function tests, renal biopsy changes and clinical manifestations, and to assess its value in determination and prediction of lupus nephritis and activity.

CHAPTER (I)

SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder in which the body's immune system incorrectly attacks the body's own tissues and organs, leading to inflammation and damage. Lupus most commonly affects women of childbearing age but also occurs in children, adolescents, and men. The cause of lupus is unknown, but it has been associated with genetic, environmental, and infectious causes. The disorder may affect almost all organs in the body, with the kidney being most commonly involved. The disorder may be mild in some cases (for example, only involving the skin) and very severe in other cases (affecting multiple organs, including the brain). The disease course is characterized by flares (intervals of active disease) and remissions (intervals of inactive disease) **(Ringold, 2006).**
It is considered as a devastating systemic autoimmune disease that predominantly affects young women, more common in African-Americans than in whites, and results in poor quality of life. Lupus has no cure, and up to 90% of patients require corticosteroids for disease control. More than half of patients with lupus have permanent organ damage **(Petri, and Brorodsky, 2006).**

Historical Background

During the nineteenth century, lupus was considered to be a skin disease. By some accounts, the erosive nature of some of the skin lesions seemed to resemble the damage inflicted by the bite of a wolf, which may have led to the name lupus (Latin word). The term erythematosus (from the Greek word for red) refers to the color of the rash, and the term systemic is used because the disease can affect organs and tissue throughout the body.

In 1872, **Moriz Kaposi** described systemic symptoms in association with cutaneous disease. At the turn of the century, Sir William Osler described arthritis and visceral manifestations in conjunction with polymorphic skin lesions. The presence of circulating immunologic factors became apparent about 50 years later with the discovery of LE cell phenomenon by **Hargrves in 1948**, the recognition of the LE factor as an ANA in 1953, and the identification of antibodies to native DNA in 1956 **(Robbins et al., 1957).**

In 1957, **Holman and Kunkel** were among the first to describe autoantibodies directed against nuclear particles by use of an immunoflurescent technique **(Seigel et al., 1970).**

Identification and characterization of abnormal autoantibodies continue to be major areas of clinical and immunological interest. The development of sensitive laboratory tests for autoantibodies has enabled the recognition of milder forms of SLE, with a consequent change in both reported prevalence and prognosis. The broad

clinical spectrum of SLE challenges the diagnostic and therapeutic acumen of the physicians **(Ropes, 1976).**

Epidemiology:

- **In the U.S.A**: Because of variable reporting, the overall prevalence ranges from 14.6-50.8 cases per 100,000. Incidence varies from 1.8-7.6 cases per 100,000 per year.
- **In Italy**: The prevalence of SLE in the district was 57.9/100 000, and Annual incidence in 2002 was 2.6/100 000. **(Gordon et al, 2005).**

- I**nternationally**: Incidence varies worldwide. In Northern Europe, it has been reported to be 40 cases per 100,000. **(David et al, 2006).**

There is a female: male ratio of approximately6-10:1, with a peak incidence between the ages of 15 and 40. However, SLE can affect all age groups, from infants to geriatric patients. **(Gordon et al, 2005).**
All races may be affected, with an apparently higher prevalence in several dark skinned racial groups **(Scballer, 1997).**

Pathogenesis:

Multiple factors are involved in the pathogenesis of SLE, i.e. genetic, immunological, hormonal, viral and environmental factors. The precise etiology of SLE, however, is unknown. An important role for genetic predisposition is suggested by the concordance of SLE in identical twins (20-50%) and dizygotic twins (5%) **(Mok**

and Lau, 2003). Many different genes have been demonstrated to contribute to disease susceptibility. However, in some patients a single gene could be responsible, as reported for homozygous deficiency of C1q, the first component of the classic pathway of complement activation **(Walport et al, 1998).** Numerous immunologic abnormalities have been distinguished in patients with SLE, all concerning immune dysregulation related to the loss of self-tolerance, as characterized by B-cell hyperactivity, autoantibody production, and immune complex formation **(Oates and Gilkeson, 2004).** The central immunological disturbance in patients with SLE is autoantibody production. Autoantibodies against a variety of self-antigens can be detected in sera of patients with SLE. An important group of autoantibodies is directed against nucleosomes and their different elements. Anti-nuclear antibodies occur in >95% of SLE patients and anti-dsDNA antibodies are the characteristic autoantibodies found in patients with SLE **(Siegert et al, 1993).**

The pathogenesis of SLE is complex target tissue damage is caused by pathogenic autoantibodies, immune complexes, and T-lymphocytes, and the abnormal immune response that permits persistence of pathogenic B and T cells has multiple components that include processing of both external and self antigens by antigen-presenting cells with hyperactivation of T and B cells and failure of multiple regulatory networks to interrupt this process, the immunologic abnormalities occur in a framework of interactions between multiple genes **(Casciola-Rosen and Anhalt., 1994)** and environmental stimuli at least one of which (ultraviolet light) can induce apoptosis in dermal cells that results in presentation of RNA

protein,DNA protein, and phospholipids self antigens to immune system **(Vaishnaw et al,1997).**

Pathology:

Blood vessels:

The onion lesions are found in the splenic arterioles in 15% of patients. These changes are due to concentric periarteriolar fibrosis thought to be the end stage of an earlier focal artritis**. (Rothfield, 1985).**

Skin:

Skin lesion in SLE demonstrates inflammation and degeneration at dermal-epidermal junction with the basal germinal layer as the primary site of injury. Necrotizing vasculitis involving small and medium sized vessels may also cause skin lesions **(Pisetsky, 2001).**

Muscles:

Examination of muscle biopsy specimen may reveal some non specific perivascular mononuclear infiltrates. **(Schur, 1986).**

Lymph Nodes:

lymph nodes may show non specific changes such as follicular hyperplasia. The thymus often shows atrophy. **(Schur, 1986).**

Heart:

Libman-Sacks verrucous endocarditis is a rare and characteristic lesion of SLE, they are found most frequently on the under surface of the posterior leaflet of the mitral

valve from where they can extend to the chordae tendinae and the mural endocardium **(Carette, 1988).**

Brain:

Brain changes are usually minimal and consist of perivascular infiltrates or micro hemorrhages **(Schur,1986).**

Kidneys:

In addition glomerular changes can have characteristics and that may help in distinguishing lupus nephritis from other forms of glomrulonephritis.

Hematoxyline bodies, the onion-skin lesions of the splenic vessels and Libman-Sacks verrucous endocarditis are the three histologic lesions most characteristic of SLE.

Hematoxyline bodies, globular masses of bluish dense homogenous material, may be scanned on hematoxyline and eosin stain. They are identical to the inclusion bodies of LE cells and the central body of LE rosettes. They can be found in all organs and are considered most characteristic of SLE. Hematoxyline bodies are formed as a result of the interaction of antibodies to nucleoprotein of cell nuclei **(Alacron Segovia, 1988).**

Etiology:

Genetic factors:

The role of genetics in SLE is supported by the moderately high concordance rate (about 30%) of SLE among monozygotic twins. Families of patients with SLE have a high prevalence of other autoimmune diseases as well, suggesting a genetic disturbance of the immune system.