



Renal Affection in Antiphospholipid Antibody Syndrome

Essay

Submitted for the Partial Fulfillment of Master Degree
In "*Internal Medicine*"

By

Aziza Mohamed Ahmed Barakat
M.B.B.Ch.

Under Supervision of

Prof. Dr. Mervat Mamdouh Abu Gabal

*Professor of Internal Medicine and Rheumatology
Faculty of medicine – Ain Shams University*

Prof. Dr. Howaida El Sayed Mansour

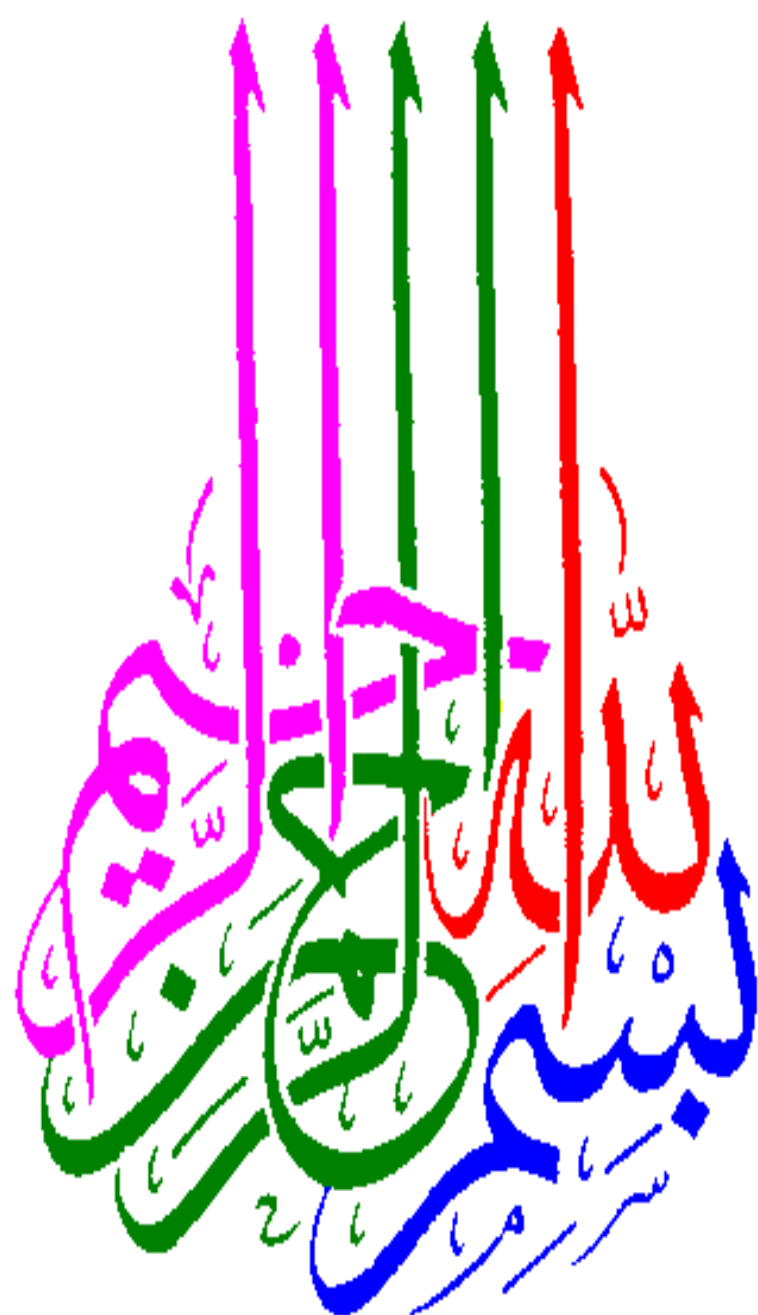
*Professor of Internal Medicine and Rheumatology
Faculty of Medicine, Ain Shams University*

Dr. Noha Hussein Ahmed Shedid

*Lecturer of Internal Medicine
Faculty of Medicine, Ain Shams University*

**Faculty of Medicine
Ain-Shams University**

2013





Acknowledgements

First of all, thanks to **Allah**, the Most Gracious, Most Merciful, for any success in achieving any work in my life, and for guiding me through and giving me the strength to complete this work the way it is.

I would like to express my deepest thanks, gratitude and appreciation to our **Prof. Dr. Mervat Mamdouh Abu Gabal**, Professor of Internal Medicine and Rheumatology, Faculty of medicine, Ain Shams University, to whom I am greatly indebted and deeply grateful for her constant supervision and encouragement together with her valuable suggestions. She gave me much of her unlimited experience which helped me to perform this work.

Words fail to express my sincere thanks and appreciation to **Prof. Dr. Howaida El Sayed Mansour**, Professor of Internal Medicine and Rheumatology, Ain Shams University, for her generous encouragement, valuable suggestion, good support, meticulous continuous supervision and unlimited help during this work.

I am really grateful and indebt to **Dr. Noha Hussein Ahmed Shedin**, Lecturer of Internal Medicine, Faculty of medicine, Ain Shams University, for her kind supervision, support and help and her continuous guidance, correction and explanation.

Last but not least I would like to express my endless gratitude to my dear husband who provided me with the valuable papers and sources for this essay. Without his help i would not have been able to complete this work.

Aziza Mohamed Ahmed Barakat
2013

List of Contents

Title	Page
List of Abbreviations	--
List of figures	--
List of Tables	--
- Introduction and aim of the work	1
- Chapter (1): Antiphospholipid Syndrome	5
- Chapter (2): Renal Affection in APS	89
- Chapter (3): Management of APS	121
- Summary and Conclusion	170
- Recommendations	172
- References	174
- Arabic Summary	—

List of Abbreviations

Abs	Antibodies
ACCP	American college of chest physicians
ACL	Anticardiolipin
ANA	Antinuclear antibodies
aPA	Antiphospholipid antibodies
APASS	Antiphospholipid antibody& stroke study
APC	Activated protein c
APS	Antiphospholipid antibodies syndrome
APSN	Antiphospholipid antibodies syndrome nephropathy
APTT	activated Partial thromboplastin time
ARDS	Adult respiratory distress syndrome
ARF	Acute renal failure
ASA	Acetyl salicylic acid
BAFF	B-cell lymphocyte-activating factor
B2GP1	Beta2 glycoprotein 1
BFGF	Basic fibroblast growth factor
BUN	Blood urea nitrogen
C3	Complement3
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
CAPS	Catastrophic antiphospholipid syndrome
CBC	Complete blood count
CD4	Colony differentiating cell
CH50	Chromosome 50

CI	Confidence interval
CI	Cardiac index
CK	Creatine kinas
CNS	Central nervous system
CRF	Chronic renal failure
CRP	C reactive protein
CT scan	Computerized tamografy scan
CVD	Cardiovascular diseases
CVS	cerebrovascular strok
DIC	Disseminating intravascular coagulopathy
DRVVT	Dilute Russell's viper venom time
DRw53	Type of HLA linked antigen
dsDNA	Double stranded DNA
DVT	Deep venous thrombosis
ELISA	Enzyme linked immunosorbant assay
EPCR	Endothelial protein c receptor
ESR	Erythrocyte sedimentation rate
ESRD	End stage renal disease
EVB	Epstein Bar virus
FDA	Food and drug association
FSGS	Focal segmental glomerulosclerosis
GMB	Glomerular basement membrane
GMT	Glomerular microthrombosis
GP1b	Glycoprotein 1b
HCV	Hepatitis c virus
HDL	High density lipoprotein
HIV	Human immunocompromising virus

HLA	Human leukocyte antigen
Hit	Heparin induced thrombocytopenia
HMG-COA	Hydroxy methyl gluteryl COA
HRT	Hormonal replacement therapy
HUS	Hemolytic uremic syndrome
ICU	Intensive care unit
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMT	Intima media thickness
INR	International normalizing ratio
ITP	Idiopathic thrombocytopenic purpura
IUGR	Intra uterine growth retardation
IVIGS	Intra venous immunoglobulins
KCT	Kaolin clotting time
LA	Lupus anticoagulant
LDH	Lactic acid dehydrogenase
LDL	Low density lipoprotein
LMWH	Low molecular weight heparin
LN	Lupus nephritis
LPS	Lipopolysaccharides
LR	Livido reticularis
Lys3117-thr318	Lysine3117-thrombin3118
MI	Myocardial infarction

MN	Membranous nephritis
MPGN	Mesangioproliferative glomerulonephritis
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NO	Nitric oxide
OKT3	ortho kung-t3
OXLDL	Oxidized low density lipoprotein
P38 MAPKI	P38 mitogen activated protein kinase inhibitor
PAPS	Primary Antiphospholipid antibodies syndrome
PE	Pulmonary embolism
PF4	Platelet factor 4
PFO	Patent foramen ovals
PGS	Prostaglandins
PT	Prothrombin time
PTFTE	Polytetra fluorethylene
PVR	Pulmonary vascular resistance
RAP	Right arterial pressure
RAPS	Renal diseases in APS
RAS	renal artery stenosis
RCTs	Randomized clinical trails
RPR	Rapid plasma regain
RSFL	Recurrent spontaneous fetal loss
SF-36	The short form-36
SLE	Systemic lupus erythematosus
TF	Tissue factor
TFPI	Tissue factor growth inhibitor

TGS	Triglycerides
TIAS	Transient ischemic attacks
TLR-4	Toll like receptor-4
TMA	Thrombotic microangiopathy
TNF	Tissue necrotizing factor
TNF- α	Tumor necrosis factor- α
TPA	Tissue plasminogen activator
TTI	Tissue thromboplastin inhibition test
UV Light	Ultra violet light
UVB	Ultra violet band
VEGF	Vascular endothelial growth factor
VKA	Vitamin k antagonist
VDRL	Venereal diseases research laboratory
VS	Versus
VTE	Venous thrombotic event
WHO	World health organization

List of Figures

Figure	Title	Page
1	Diagram of the cell membrane lipid bilayer. The proteins are embedded inside of the cell membrane. The lipid content of the membrane allows the cell membrane to automatically repair itself when it is torn.	19
2	Schematic representation of the hypothesis that anti- β 2-GPI Abs in complex with β 2-GPI may be able to amplify the production of autoantibodies via their ability to bind and crosslink TLR4	25
3	Livedo reticularis	46
4	Gangrene of distal extremities	46
5	Splinter hemorrhage under the nails.	47
6	Valvular thickening and thrombosis in a prosthetic mitral valve of a patient. With primary APS	49
7	Triggers of CAPS	57
8	APS relationship to SLE Multiple Manifestations in SLE& APS	61
9	Glomerulus showing extensive mesangiolysis (arrowhead) and intracapillary fibrin thrombi (arrows)	95
10	Interlobular artery showing striking fibro elastic intimal thickening with almost complete obliteration of its lumen	95
11	Renal vein thrombosis	108
12	Renal artery stenosis in APS	109
13	Right renal artery stenosis associated with hypertension in antiphospholipid syndrome.	110
14	Renal vein thrombosis	112
15	Glomerulus showing reduplication of the capillary basement membrane	113

List of Tables

Table	Title	Page
1	Different aPA specificities	8
2	Proposed mechanisms by which anti- phospholipid antibodies might induce an increased risk of thrombosis and foetal loss	27
3	Antiphospholipid antibodies in various infections	31
4	Risk factors for thrombosis	36
5	Cardiac manifestations in APS	50
6	Renal manifestations in antiphospholipid syndrome	93
7	The main histological features in antiphospholipid syndrome nephropathy	96
8	Specific therapies	135
9	Proposed Management for Women With aPA Antibodies	145
10	Potential current and future treatments for antiphospholipid syndrome	158

Introduction

The antiphospholipid syndrome (APS) is characterized by antibodies directed against either phospholipids or plasma proteins bound to anionic phospholipids. Patients with the APS may display a constellation of clinical features including venous and arterial thrombosis, recurrent fetal losses, and thrombocytopenia **(Kumar and Roubey, 2010)**.

Antiphospholipid antibodies associated with vaso-occlusive events without any underlying disease process is termed the primary antiphospholipid antibody syndrome (PAPS). The presence of antiphospholipid antibodies and a vaso-occlusive event superimposed on an underlying disease, such as SLE or malignancy, and drugs, is a secondary antiphospholipid antibody syndrome **(Erkan and Lockshin, 2009)**.

Four types of antiphospholipid antibodies have been characterized:

- Antibodies causing a false positive VDRL,
- Lupus anticoagulants,
- Anticardiolipin antibodies,
- And Antibodies to beta2-glycoprotein I **(Kumar and Roubey, 2010)**.

Catastrophic antiphospholipid antibody syndrome is a serious, often fatal form of the disease; it is associated with

Introduction and Aim of the Study

multiple organ infarctions. Death may occur within days or weeks (**Bucciarelli et al., 2009**).

The kidney is one of the organs that can be compromised in patients with antiphospholipid antibodies (aPA). APSN (antiphospholipid antibody syndrome nephropathy) is an early clinical marker of APS. Renal complications directly resulting from thrombotic events associated with these antibodies include glomerular disease, large vessel renal involvement, and coagulation problems relating to dialysis and renal transplants. The most prominent symptoms and signs are edema, foaming urine, hypertension, or a combination.. The earliest symptom being inhibition of glomerular filtration. Clinical combinations of the symptoms allow to distinguish variant of APSN suggesting the existence of acute and chronic APSN (**Shilov et al., 2003**).

In patients with end-stage renal disease, antiphospholipid antibodies are prevalent and may increase in frequency with time on dialysis, possibly as a result of oxidative stress incurred during dialysis (**Erkan and Lockshin, 2009**).

In primary and secondary APS combination of antiphospholipid antibody syndrome nephropathy (APSN) with impairment of the CNS, heart and skin, correlation of its basic clinical manifestations with arterial thrombosis allow us to single out a special clinical variant of APS manifesting with generalized ischemic lesions of the organs as a result of arterial/arteriolar thrombosis. Irrespective of its nature, APSN has common characteristic features combination of arterial hypertension, persistent renal dysfunction and transitory hypercreatininemia, correlating with development of arterial

Introduction and Aim of the Study

thrombosis; therefore, this pathology can be considered as a variant of thrombotic vascular lesion of the kidneys **(Kozlovskaja et al., 2007)**.

The thrombotic process in the intra renal vessels in PAPS dictates the necessity to develop novel approaches to treatment of such patients. In addition to immunodepressants the treatment should include indirect anticoagulants and antiaggregants **(Ioannou et al., 2008)**.

Aim of the Study

Is to review the most recent literatures and researches concerning the renal affection in antiphospholipid antibody syndrome to help to improve the patient outcome.