TO FIND OUT THE ASSOCIATION OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME AND CHRONIC LEG ULCERS.

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF M.D.DERMATOLOGY, VENEREOLOGY & LEPROSY

DEPARTMENT OF DERMATOLOGY, VENEREOLOGY & LEPROSY
PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH
THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY
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APRIL 2012
This is to certify that the dissertation entitled “TO FIND OUT THE
ASSOCIATION OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME AND CHRONIC LEG
ULCERS.” is a bonafide work of Dr. Sheja Arul done under my direct guidance and
supervision in the Department of Dermatology, Venereology and Leprosy, PSG
Institute of Medical Sciences and Research, Coimbatore in fulfillment of the
regulations of Dr. M.G.R Medical University for the award of MD degree in
Dermatology, Venereology and Leprosy.

Dr. Reena Rai MD,
GUIDE

Dr. C.R. Srinivas MD,
HEAD OF DEPARTMENT

PRINCIPAL
DECLARATION

I hereby declare that this dissertation entitled **“TO FIND OUT THE ASSOCIATION OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME AND CHRONIC LEG ULCERS”** was prepared by me under the direct guidance and supervision of Professor Dr. Reena Rai MD, PSG Institute of Medical Science and Research, Coimbatore.

The dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University in fulfillment of the University regulations for the award of MD degree in Dermatology, Venereology and Leprosy. This dissertation has not been submitted for the award of any other Degree or Diploma.
Acknowledgement

I wish my sincere thanks to our **Dean Dr. Ramalingam MD, PRINCIPAL, PSG Institute of Medical Sciences and Research, Coimbatore**, for permitting me to work on this dissertation and avail all the facilities at this institution.

I am deeply indebted to our **Chief Prof. Dr. C. R. Srinivas MD, Professor and Head of Department of Dermatology, Venereology and Leprosy, and Prof. Dr. Reena Rai MD** my guide for whose guidance this study would not have come through. It has been a great privilege to work under them.

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I express my heartfelt thanks to Mr. M. Thirumoorthy, Mrs. Shanthi, Mrs. Rajeshwari and Miss. Krithika for their help and support.

This study would not have seen the light of the day, had not our **patients** showed kind co-operation. I sincerely thank them.
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ANTIPHOPSPHOLIPID ANTIBODY SYNDROME

HUGHES SYNDROME

Introduction:

Antiphospholipid antibody syndrome (APS) is characterized by the presence of antiphospholipid antibodies (APLA), recurrent thrombosis and fetal loss. Antiphospholipid antibodies are a family of auto antibodies that recognize various combinations of phospholipids, phospholipid-binding proteins or both. The exact pathogenic mechanism in which these antibodies cause thrombosis is not known. This syndrome is termed as primary APS when it occurs in the absence of underlying or associated disease. Secondary APS is associated with autoimmune diseases such as systemic lupus erythematosus. Clinical features can vary widely and can involve any organ system but the features for both primary and secondary APS are identical. In primary APS, dermatological manifestations are probably the most common and 40% of the patients may have cutaneous feature as the major complaint. Skin manifestations may be the first clue to this syndrome and it is important to be aware and investigate the possibility of APS when facing cutaneous findings related to venous or arterial thrombosis or microthrombosis.
AIM AND OBJECTIVES:

To find out the association of Antiphospholipid antibody syndrome and chronic leg ulcers.
REVIEW OF LITERATURE

HISTORY:

In 1906, the first antiphospholipid antibody, a complement fixing antibody that reacted with extracts from bovine hearts was detected in patients with syphilis\(^1\). The antigen was identified as cardiolipin mitochondrial phospholipid. This observation became the basis for the venereal disease research laboratory (VDRL) test for syphilis. It was later established that many patients with SLE had positive test to VDRL without serological evidence for syphilis. In 1983 Harris & Co-workers described a radioimmunoassay for the estimation of anti-cardiolipin\(^2\). 2 years later they developed the first ELISA for the quantitative detection of anti cardiolipin antibody. Harris and his colleagues in 1986 called this the “Antiphospholipid Syndrome” \(^3\). Asherson introduced the term primary Antiphospholipid syndrome to describe patients with APS without an underlying disorder. Hughes et al recognized that the features of anti phospholipid antibody syndrome existed with non-lupus patients\(^4\). In 1990s it was discovered that some anticardiolipin antibodies require the presence of plasma phospholipid binding protein β2-glycoprotein I (β2GPI) in order to bind to cardiolipin\(^5,6\). The demonstration that anticardiolipin antibodies are directed against a phospholipid –binding protein rather than phospholipids led
to the discovery that some auto antibodies bind directly to β2glycoprotein 1 in the absence of phospholipids. This has resulted in a change of focus from phospholipid to phospholipid binding protein.

**EPIDEMIOLOGY:**

Several antiphospholipid studies have been conducted in order to establish the prevalence of antiphospholipid. APLA are found in 1% and 5%\(^\text{(7)}\) of healthy persons. APLA in apparently healthy individuals is low titre and transient. Among patients with SLE, the Prevalence of APLA is much higher, ranging from 12% to 30\(^\text{(8,9)}\) for anticardiolipin antibodies, and 15% to 34% for lupus anticoagulant antibodies\(^\text{(9)}\). APS may develop in 50 to 70% of patients with both systemic lupus erythematosus and APLA after 20 years of follow up\(^\text{(7)}\). Most studies reported a higher prevalence of APLA in elderly than in younger adults.

**Race:**

No defined racial predominance for primary antiphospholipid antibody has been documented.

**Sex:**

A female predominance has been documented, particularly for secondary antiphospholipid antibody syndrome.
Age:

APS is common in young to middle-aged adults. Children and elderly people can also be affected. Disease onset has been reported in children as young as 8 months.

GENETIC FACTORS:

Familial cases of lupus anticoagulant and anticardiolipin antibody also have been reported\(^\text{[10,11,12]}\) whether family members of patients with antiphospholipid antibody syndrome are more likely to have APLA’s or autoimmune disease, and whether this results from an autosomal-dominant autoimmune gene that is incompletely penetrated is under study. Multiple HLA-DR or DQ association with APLA has been described.

PATHOGENESIS:

MECHANISM OF HEMOSTASIS:

Hemostasis is maintained in the body by various mechanisms which when perturbed clotting results. Anti clotting mechanism in the body operates against intravascular coagulation. Heparin is a natural anticoagulant produced by the liver. Thrombomodulin produced by the endothelium of the blood vessels. Thrombomodulin is a thrombin binding protein binds with thrombin and forms thrombomodulin Thrombin-Thrombin complex. This complex
activates protein C. Activation of Protein C along with its cofactor protein S inactivates factor V and VIII. Inactivation of these two factors prevents clot formation.

Endothelial derived Nitric oxide has been shown to inhibit platelet adhesion and aggregation. PGI$_2$, secreted by Endothelium inhibits platelet adhesion and aggregation.

**MECHANISM OF HEMOSTASIS – NORMAL**

**SITES AFFECTED IN APLA**

Phospholipids are a class of polar lipids composed of a phosphate and one or more fatty acid molecules produced in all types of all in the body. This phospholipids found in the tissue are either anionic (phosphotidyl serine, phosphotidyl ionositol, phosphatidic acid and cardiolipin) or neutral (phosphotidyl choline & phosphotidyl ethanolamine). But antiphospholipid antibodies are directed against a variety of phospholipid – binding protein such as β2gpl, prothrombin , protein C and S$^{(13)}$.  

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$^{(13)}$References ignored for brevity.
Mechanism by which antiphospholipid antibodies promote thrombosis:

1. Interference with Coagulation cascade:

Phospholipids are present at several points in the extrinsic, intrinsic and common pathway of coagulation cascade. Phospholipids are necessary for activation of factor X in the intrinsic pathway, activation of factor IX & X in the extrinsic pathway and conversion of prothrombin to thrombin in the final or common pathway. APLA interfere with the function of phospholipid binding protein involved in the regulation of coagulation leading to hyper coagulation state by the following mechanisms.

a) Interaction of anticardiolipin with β2GPI bound to phospholipid inhibits protein c, protein s, which are natural anticoagulants\(^{(14)}\).

b) APLA binds to thrombin activated platelets, inhibiting thrombin –mediated endothelial cell prostacyclin release or inhibiting protein C activation\(^{(15)}\).

C) Autoantibodies to a variety of Endothelial cell surface proteins including thrombomodulin, heparin sulfate and Heparin sulfate proteoglycan have been described.
IgG antiphospholipid antibodies that react with heparin sulfate have been shown to inhibit the formation of anti-thrombin III complexes that could contribute to vascular thrombosis\textsuperscript{(16)}.

D) Antibodies against platelet activating factor in patients with autoimmune disease and antiphospholipid antibody syndrome\textsuperscript{(17)}.

2) Activation of Endothelial cells:

Antiphospholipid antibody recognize β2GPI to resting endothelial cells, binding causes activation of endothelial cells with up-regulation of cytokines and adhesion molecules with metabolism of Prostacyclin resulting in hypercoagulation\textsuperscript{(18)}. 
3) Oxidant mediated injury of the vascular Endothelium:

Oxidized low–density lipoprotein, is a major contributor of atherosclerosis, is taken up by macrophages leading to macrophage activation and subsequent damage to endothelial cells\(^{(19)}\). Anticardiolipin antibodies binds to oxidized cardiolipin, suggest that APLA recognize oxidized phospholipid binding protein thus contributing to hypercoagulation.

4) Genetic:

There is a familiar association and relatives of persons with known Antiphospholipid antibody syndrome are more likely to have antiphospholipid antibodies.

**PATHOGENESIS OF ANTIPHOSPHOLIPID IN PREGNANCY:**

Passive transfer of maternal antibodies mediates autoimmune disorder in the fetus and newborn.

APLA inhibit production of placental prolactin, insulin like growth factor, signal transducer and activator of transcription 5 and they adversely affect formation of trophoblast syncytium, placental apoptosis and trophoblast invasion\(^{(20)}\) all processes required for normal establishment of placental function.

It is hypothesized that complement activation is necessary event in the pathogenesis of fetal loss associated with APS. Activated complement
fragments themselves and have the capacity to and activate inflammatory and endothelial cells as well as induce a prothrombotic phenotype, either directly through the membrane attach complex or through c5a receptor (CD88)-mediated effects\(^{(21,22)}\). Circulating antiphospholipid antibodies activates complement and initiating a signaling cascade which induces platelet to aggregate and initiate thrombosis\(^{(23)}\).

![Diagram of clot formation in APLA](image)

Antiphospholipid antibody competes in the placenta for phosphatidylserine and annexin 5, possibly interrupting a shield that is thought to protect the fetus from maternal prothrombotic mechanism\(^{(24,25)}\).

**Mechanism of clot formation in APLA:**

APLA interact with endothelial cells, through binding of β\(_2\)GPI on the cell surface inducing a procoagulant and proinflammatory endothelial also upregulates tissue factor expression on endothelial cells and blood monocytes, and promote endothelial leukocyte adhesion, cytokine secretion and PGE\(_2\) synthesis. APLA recognize phospholipid-binding proteins expressed on
platelets and potentiates platelet aggregation. APLA affects fibrinolysis and binding of the natural anticoagulant annexin A5 to anionic structures. These mechanisms all contribute to a procoagulant state that is necessary but not sufficient for clotting. Clot formation seems to require two steps: the presence of APLA provides the 'first hit', which produces clotting when accompanied by another procoagulant condition, like infection a 'second hit'. Complement activation seems to be necessary for clot formation.

PICTURE 1: MECHANISM OF CLOT FORMATION IN APS:
Classification of APLA:

APLA is termed as primary when it occurs in the absence of underlying disease.

Secondary APLA is associated with autoimmune disease such as SLE.

Criteria for diagnosis of APLA:

Classification with APS requires evidence of both one or more specific, documented clinical events (either a vascular thrombosis and/or adverse obstetric event) and the confirmed presence of a repeated APLA. The Sapporo APS classification criteria (1998, published in 1999) were replaced by the Sydney criteria in 2006. Based on the most recent criteria, classification with APS requires one clinical and one laboratory manifestations

Clinical:

- A documented episode of arterial, venous, or small vessel thrombosis—other than superficial venous thrombosis in any tissue or organ by objective validated criteria with no significant evidence of inflammation in the vessel wall and/or
- 1 or more unexplained deaths of a morphologically normal fetus (documented by ultrasound or direct examination of the fetus) at or beyond the 10th week of gestation and/or 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation,
with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded or at least 1 premature birth of a morphologically normal neonate before the 34th week of gestation due to eclampsia or severe pre-eclampsia according to standard definitions, or recognized features of placental insufficiency plus

**Laboratory:**

- Anti-cardiolipin IgG and/or IgM measured by standardized, non-cofactor dependent ELISA on 2 or more occasions, not less than 12 weeks apart; medium or high titre (i.e., > 40 GPL or MPL, or > the 99th percentile) and/or

- Anti-β2 glycoprotein I IgG and/or IgM measured by standardized ELISA on 2 or more occasions, not less than 12 weeks apart; medium or high titre (> the 99th percentile) and/or

- Lupus anticoagulant detected on 2 occasions not less than 12 weeks apart according to the guidelines of the International Society of Thrombosis and Hemostasis.

- Test should be repeated every 5 years.
CLINICAL PRESENTATIONS:

Introduction

Clinical features of APS can vary widely and can involve any organ system but the features for both primary and secondary APS are identical. In primary APS, dermatological manifestations are most common. 41% of patients can have skin lesions as the first sign of disease\(^\text{(26)}\). Multisystem thrombotic events develop in patients with cutaneous manifestations of antiphospholipid antibody syndrome. First common cutaneous manifestations is livedo reticularis\(^\text{(27)}\). Livedo reticularis presents as painful violaceous macules or papules often occurs in a net like pattern with tendency to ulcerate and heals with atrophic scar. Usually seen over ankles, dorsa of feet and may extend to lower legs. It is the hallmark manifestations of APLA it’s a neurodermatologoical disorder. It is commonly associated with Sneddens syndrome (livido reticularis and ischemic cerebrovascular lesions).

The Second cutaneous manifestation is non-healing leg ulcerations which are usually chronic, painful, recurrent and necrotic usually involves the lower extremities\(^\text{(28)}\). Leg ulcers often resemble pyoderma gangrenosum\(^\text{(29)}\). Pathology behind leg ulcer includes vascular thrombosis, capillary proliferation, endarteritis obliterans and lymphocytic infiltration\(^\text{(30)}\).
Other cutaneous manifestations reported are cutaneous necrosis\textsuperscript{31,32,33} digital gangrene, atrophic blanche, raynaud’s phenomenon, acrocyanosis, splinter hemorrhages, bullous SLE, rheumatoid nodules, digital gangrene, Venous thrombosis, anetoderma, auto immune blister disease, granuloma, pyogenicum and intestinal granulomatous dermatitis. (Table 1)

Table 1:

<table>
<thead>
<tr>
<th>Skin manifestations of antiphospholipid antibody syndrome</th>
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<td>Livido reticularis</td>
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<td>Ulceration</td>
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<td>Digital gangrene</td>
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<td>Subungual splinter hemorrhage</td>
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<td>Primary anetoderma</td>
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<tr>
<td>Extensive cutaneous necrosis</td>
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<tr>
<td>Thrombocytopenic purpura</td>
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<tr>
<td>Livedoid vasculitis</td>
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<tr>
<td>Atrophic blanch</td>
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<td>Pterygium ungium</td>
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PICTURE 2: CHRONIC NON HEALING ULCER WITH NECROTIC SLOUGH

PICTURE 3: CHRONIC NON HEALING ULCER OVER MEDIAL MALLEOLUS
PICTURE 4: CHRONIC NON HEALING ULCER WITH SLOUGH

PICTURE 5: CHRONIC NON HEALING ULCER INVOLVING THE WHOLE LEFT LOWER LIMB
SYSTEMIC INVOLVEMENT:

1 VENOUS THROMBOSIS:

Deep vein thrombosis\(^{(34)}\). Thrombosis is also seen in retinal, renal, superior mesenteric\(^{(35)}\), splenic \(^{(36)}\) and hepatic veins \(^{(37)}\). In patients with antiphospholipid antibody, venous thrombosis is recurrent\(^{(38)}\). Few patients can also present with both arterial and venous thrombosis. Cerebral and peripheral arterial thrombosis is also seen in patients with APLA.

2 NEUROLOGIC SYNDROME:

Most commonly encountered event in patients with APLA includes stroke, focal cerebral ischemia, ocular ischemia, transverse myelopathy, complicated migraines, chorea, seizures, apnea, multi infarct dementia, ischemic encephalopathy, pseudo tumor cerebri, transient global amnesia. APLA binds to brain tissue, inhibits astrocyte proliferation and depolarize brain nerve terminals. Cerebral infarcts\(^{(39,40)}\) in antiphospholipid antibody syndrome can occur in any territory and have been found in both the anterior and posterior circulation. Stroke in APS often multiple recurrent can lead to multiple infarct dementias. Encephalopathy and cerebral atrophy after infarct has also been reported.
3 SNEDDONS SYNDROME:
Sneddons syndrome was first described by Levine and Welch. It is a disorder common in females, characterized by livedo reticularis and ischemic cerebrovascular lesions\(^{(41)}\). It is a genetic disease with autosomal dominance. Livedo reticularis may precede the onset of stroke by years, and the ischemic events are usually repeated.

4 MULTIPLE SCLEROSIS:
Multiple sclerosis in antiphospholipid antibody syndrome is seen mainly over putamen\(^{(42)}\).

5 TRANSVERSE MYELOPATHY:
Lupoid sclerosis is a syndrome in Systemic lupus erythematosus in which neurologic events such as optic neuritis and transverse myelitis occur resembling multiple sclerosis. Studies\(^{(43)}\) had found that most of the patients with SLE with transverse myelitis had antiphospholipid antibodies.

6 OCULAR SYMPTOMS:
Amourosis fugax, retinal artery occlusion\(^{(44)}\), occlusive vascular retinopathy, retinal vein occlusion\(^{(45,46)}\) and ischemic optic neuropathy\(^{(47)}\). Young patient if present with retinal artery occlusion should be investigated for APLA.
7 MIGRAINE:

Recurrent and severe migraine episodes are reported. Few studies reported that increase incidence of cerebral infarcts in patients with migraine\(^{(48)}\). Apnea, brain stem dysfunction, chorea hyperactivity and cognitive dysfunction have also been reported.

8 CARDIAC MANIFESTATIONS:

Angina, myocardial infarction is the commonest cardiac manifestation seen in patients with antiphospholipid antibody syndrome. Cardiac manifestations are less frequent than neurologic and arterial events\(^{(49)}\). There is an increased prevalence of valve vegetations and mitral regurgitation in patients with antiphospholipid antibody syndrome. Other cardiac manifestations are coronary vasculopathy, intra cardiac thrombus and atherosclerosis.

9 PREGNANCY MANIFESTATIONS:

The most specific association of antiphospholipid antibody syndrome is with mid trimester pregnancy loss\(^{(50,51)}\), pre-eclampsia\(^{(52,53)}\), hemolysis, elevated liver enzyme and low platelet (HELLP syndrome)\(^{(54,55)}\) and thrombo embolism. Antiphospholipid antibody syndrome can lead to abortions, preterm labor, intra uterine growth retardation and intra uterine death.
Infertility:

Several studies have suggested an increase in antiphospholipid antibodies in infertility\(^{(56)}\). Proposed mechanism behind infertility includes abnormal implantation, placentation and embryonic vascular compromises. Studies reported that improved outcome with heparin treatment in APS positive women undergoing In vitro fertilization.

10 PULMONARY MANIFESTATIONS:

Pulmonary emboli are the frequent complication of deep venous thrombosis in patients with APS.

Pulmonary capillaritis with hemorrhage\(^{(57)}\), pulmonary fibrosing alveolitis\(^{(58)}\), pulmonary non inflammatory vasculopathy\(^{(59)}\), pulmonary hypertension due to emboli, pulmonary artery thrombosis\(^{(60)}\) common with postpartum cases.

11 RENAL MANIFESTATIONS:

APLA can cause thrombosis of renal artery\(^{(61)}\) and vein, proteinuria, increases creatinine levels, nephropathy induced hypertension, thrombi in glomerular capillaries, severe renal impairment, intimal proliferation of small and medium sized arteries and hyalinosis of arterioles. Patients with APS commonly presented with hypertension, elevation of serum creatinine and progression of histiologic lesions on repeat biopsy.
Renal transplants:

APS may also leads to early graft rejection\(^{62}\).

12 ENDOCRINE MANIFESTATION:

Adrenal failure has been reported in many patients with APLA\(^{63,64}\).

Adrenal hemorrhage with infarction has been commonly reported\(^{65}\).

Most of the adrenal hemorrhage reported is spontaneous in onset.

Adrenal infarction after cessation of warfarin therapy has also been reported.

13 GASTROINTESTINAL MANIFESTATIONS:

Portal and hepatic vein thrombosis\(^{66}\).

14 OTHER ARTERIAL MANIFESTATIONS:

Arterial thrombi leading to digital gangrene.

15 HEMATOLOGICAL MANIFESTATION:

Hemolytic anemia, thrombocytopenia, can cause bone marrow necrosis.

Thrombocytopenia:

It is the most common manifestation of APS. APLA bind and can induce a morphologic change in platelets\(^{67}\). Thrombocytopenia in both patients with autoimmune disease and patients with chronic immune thrombocytopenia purpura is associated with anti cardiolipin antibodies.

Thrombocytopenia was more common in patients with APS who had arterial thrombosis.\(^{68}\)
Hemolytic anemia:

Both anticardiolipin antibodies and lupus anticoagulant are associated with hemolytic anemia\(^{(69,70)}\).

Bone marrow necrosis:

Rare cases of bone marrow necrosis have been reported secondary to APS\(^{(71,72)}\).

16 MUSCULOSKELETAL:

Avascular necrosis of bone has been reported in patients with APS. Catastrophic form of APLA can present with multiple sites of avascular necrosis. Primary APS usually associated with asymptomatic avascular necrosis.

17 NEONATAL MANIFESTATIONS:

Transplacental transfer of APLA antibodies can lead to umbilical cord thrombosis\(^{(73)}\), stroke, seizures\(^{(74)}\), multiple thrombosis and fetal aortic thrombosis. Placental insufficiency leading to IUGR babies.

**Catastrophic antiphospholipid antibody syndrome (CAPS):**

It’s a rare, abrupt, life threatening complication. It consists of multiple thrombosis of small and medium arteries causing stroke, cardiac, hepatic, adrenal, renal intestinal infarct and peripheral gangrene\(^{(75)}\). The commonest organ involved in CAPS is renal followed by pulmonary and brain. Acute
adrenal failure is the initial clinical event. Patients with CAPS often have thrombocytopenia, fragmented erythrocytes. Renal failure and pulmonary hemorrhage may occur.

Tissue biopsies of these patients show non inflammatory vascular occlusion.

Preliminary criteria for classification of catastrophic antiphospholipid syndrome

1) Evidence of involvement of three or more organs, systems, or tissues

2) Development of manifestation simultaneously or in less than 1 week

3) Confirmation by histopathology of small vessel occlusion in at least 1 organ or tissue

4) Lab confirmation of the presence of antiphospholipid antibody

Definite catastrophic APS – all 4 criteria

Probable catastrophic APS

Criteria 2 through 4 two organs, systems, or tissues involved

Criteria 1 through 3, except no confirmation 6 week apart due to early death of patient.

Criteria 1, 2, 4.
Criteria 1, 3 and 4 development of third event more than one week but less than one month after the first, despite anticoagulation.

**Sero negative antiphospholipid antibody syndrome (SNAPS):**

This term first coined by Mc Carty and colleagues in an abstract in 2000\(^{(43)}\).

Patients presents with clinical features that are similar to those of antiphospholipid antibody positive patients with negative antiphospholipid antibodies.

It is recommended that to make a diagnosis of SNAPS, the patients should be seronegative for all antibodies at the time of thrombotic events\(^{(76)}\).

There are 3 possibilities mentioned:

- **a)** Diagnosis may be wrong, patient has a different coagulopathy.

- **b)** Laboratory problem conventional testing failing to pick up cases

- **c)** Previous antiphospholipid titres reverted to negative, such as in Sneddon’s syndrome.

**APLA with Auto immune disease:**

APLA associated with autoimmune disease is often called secondary APS.

It is reported that APLA is seen in 50% of patients with lupus.
Comparing the diagnostic criteria for APS and American college of rheumatology, revised criteria for SLE reveal many overlapping features between APLA and Lupus. This includes proteinuria, pleuritis, thrombocytopenia, hemolytic anemia and Seizures and APLA\(^{(77)}\).

Effect of APLA on SLE is super imposed thrombotic complications like renal infarction and renal artery or vein thrombosis which can exacerbate the glomerulonephritis of SLE. Many of the earlier described Central nervous system manifestation of SLE especially seizures, stroke and transverse myelitis were most likely caused by vaso-occlusive disease of APLA and not SLE (APS). Pulmonary hypertension in patients with SLE is also more likely secondary to APS.

Other autoimmune diseases associated with APS are Sjogrens syndrome, rheumatoid arthritis, scleroderma and systemic vasculitis.
**Condition associated with antiphospholipid antibodies:**

<table>
<thead>
<tr>
<th>Common autoimmune or rheumatic diseases with apl-</th>
<th>SLE, sjogren syndrome, rheumatoid arthritis, autoimmune thrombo cytopenic purpura, autoimmune hemolytic anemia, psoriatic arthritis, systemic sclerosis, mixed connective –tissue disease, Polymyalgia rheumatic, Giant cell arteritis, Behcet syndrome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Syphilis, hepatitis c infection, HIV infection, human t-cell lymphotropic virus type 1infection, bacterial septicemia</td>
</tr>
<tr>
<td>Drugs</td>
<td>procainamide, quinidine, propranolol, hydralazine, phenytoin, chlorpromazine, interferon alfa, quinine, amoxicillin.</td>
</tr>
</tbody>
</table>
INVESTIGATIONS:

Detection of Antiphospholipid Antibodies:

Antibodies which are commonly detected are Lupus anticoagulant antibodies (LAC), anticardiolipin (ACL) and anti β2- glycoprotein I (β2-GPI) Antibodies.

Lupus anticoagulant antibodies are identified by coagulation assays in which they prolong clotting times.

Anticardiolipin antibody and Anti β2-GPI are detected by immune assay that measures immunologic reactivity to phospholipids or phospholipids binding protein.

Detection of Lupus Anticoagulant antibodies (LAC):

Lupus anticoagulants are IgG, IgM, IgA immunoglobulins, potentially cause prolongation of phospholipid-dependent coagulation tests. Lupus anticoagulant assays do not actually measure a titer of antibody, but are functional tests. Lupus anticoagulant prolongs clotting time and is measured by coagulation assays.

Coagulation abnormalities can be assessed by aPTT, aPT and platelet count as the first step \(^{(78)}\). The second step is the determination of lupus anticoagulant by demonstrating that the prolongation of screening test results from an antibody not a quantitative or qualitative coagulation factor deficit or
inhibition. Lupus anticoagulant are heterogeneous, no single test detects all lupus anticoagulant. Majority of experts now agree that two test need to be performed (one screening test and a confirmatory test).

aPTT test:

The sensitivity of the aPTT varies proportionally with the nature of commercial reagents used. aPTT is more sensitive than PT. False positive aPTT occur with clotting factor deficiency, heparin, factor VII inhibitors and factor IX/VIII deficiencies\(^{(79)}\).

**Dilute Russell Viper venom time screening and confirmatory test (dRVVT):**

Sensitive screening and confirmatory test for lupus anticoagulant\(^{(80)}\). Diagnostic test based on the ability of the venom to induce thrombosis. Coagulant in the venom directly activates factor X in coagulation cascade which converts pro-thrombin to thrombin. In case of APLA there is prolongation of clotting time. The prolongation is reversed by adding excess phospholipid to the reaction to ensure that prolongation of the clotting time is not a result of a factor deficiency, the procedure includes mixture of patient and control plasmas.

This test is useful during pregnancy as it is independent of naturally occurring increase in some clotting factors, and does not give false –positive results\(^{(81)}\).
PICTURE 6: ANTIPHOSPHOLIPID ANTIBODY DETERMINATION BY LUPUS ANTICOAGULANT.

DPT test:

This test is a dilute PT performed with varying dilution of tissue factor or thromboplastin and expressed as a ratio of patient-to-normal PT. This test assessed all three critical phospholipid–dependent coagulation reactions, it seems ideal for lupus anticoagulant screening test.

Laboratory detection of anticardiolipin antibodies (ACL):

Measurement of anticardiolipin isotypes IgG, IgM, IgA is by ELISA. IgG ACL is a major predictor of thrombosis and pregnancy loss\(^{(82)}\). IgM ACL is associated with hemolytic anemia and thrombosis\(^{(83)}\).
Kaolin clotting time (KCT):

KCT is an aPTT without added platelet substitute, with the kaolin acting as an activator and phospholipid surface. KCT is affected by residual platelet and therefore requires a filtration step to remove platelets from the patient’s plasma. False-positive results can be seen in certain conditions.

Platelet neutralization procedure:

It is one approach to proving that an inhibitor is phospholipid dependent is to neutralize the inhibitor by increasing the amount of phospholipid in the assay or to accentuate the prolonged coagulation time by reducing the phospholipid.

Skin Biopsy:

The histological pattern is thrombosis without significant evidence of inflammation in the vessel wall.

Detection of beta 2 glycoprotein I:

β2GPI also called apolipoprotein H cofactor (isotypes IgG and IgM) detected by ELISA. β2GPI has multiple roles including inhibition of platelet aggregation, activation of platelet prothrombinase activity.

Binding of autoimmune ACL antibodies is enhanced by the presence of β2GPI, as opposed to anticardiolipin antibodies that are made in response to infections. Thus, it is now possible to differentiate anticardiolipin antibody
caused by infections from those caused by autoimmunity, which are associated with antiphospholipid antibody syndrome. Anti-beta 2 glycoprotein titre of >99 percentile for two times with 12 weeks apart is considered positive.

Anti β2GPI is associated with pregnancy induced hypertension, pre-eclampsia (84) and pregnancy loss (85). Lupus anticoagulant antibodies are more specific and anticardiolipin is more sensitive test for antiphospholipid antibody syndrome.

**Doppler:**

Doppler is useful in pregnancy in early detection of thrombosis and infarction of uteroplacental vasculature. It is also useful to examine superficial and deep arterial and venous circuits.

**VDRL:**

False positive in 30-40% of patients with chronic leg ulcer when it is associated with infections. It is a transient positivity. Antiphospholipid antibodies usually became negative within 12 weeks.

**Biological false positive antiphospholipid antibody:**

**Infections:**

Syphilis (86), hepatitis C infection (86), lepromatous leprosy (86), HIV infection, human T-cell lymphotrophic virus type 1 infection, malaria, bacterial septicemia
Drugs:

Procainamide, quinidine, propranolol, hydralazine, phenytoin, chlorpromazine, interferon alfa, quinine, amoxicillin. 3% of normal persons have antiphospholipid antibodies in low titres. These are conditions where, there is a transient increase in antiphospholipid antibodies and the titers usually come down within 12 weeks and the test after 12 weeks are usually negative. Infections and drugs could cause false positive antiphospholipid antibodies by generation of an altered humoral response. False positive antiphospholipid antibodies are not associated with complications like thrombosis.

**TREATMENT OF ANTIPHOSPHOLIPID ANTIBODY SYNDROME:**

Management of antiphospholipid antibody syndrome involves primary thromboprophylaxis and secondary management of thrombo embolic events.

**Primary thromboprophylaxis:**

Primary thromboprophylaxis with low dose aspirin. Aspirin acts by inhibiting platelet aggregation. Aspirin also inhibits the activation of endothelial cell\(^{(87)}\) by antiphospholipid antibodies. There are controversies whether thromboprophylaxis is required for patients who are asymptomatic \(^{(88)}\) with antibodies remains unsolved. Low dose aspirin associated with reduction in thrombus formation\(^{(89)}\). Tablet hydroxychloroquine reduces the formation of APLA –beta 2 glycoprotein I complexes to phospholipid bilayers. It also reduces
the thrombus size, reverse platelet activation\textsuperscript{(90)}, lowers titers of APL antibodies. Quinacrine another antimalarial drug reduces anticardiolipin titers\textsuperscript{(91)}.

Other preventive measures includes

- Cessation of oral contraceptives
- Avoidance of smoking
- Treatment of hypertension, diabetes and hyperlipidemia

**Secondary Thromboprophylaxis:**

Secondary thromboprophylaxis refers to treatment initiated after the occurrence of thrombotic events to prevent further attacks. Low molecular weight heparin has been used in the initial phase followed by warfarin in the management.

**Management of acute arterial thrombosis:**

Treatment of acute arterial event in patients with antiphospholipid antibody syndrome must balance aggressive therapy to recannulate the vessel to prevent thrombosis or hemorrhagic complications. Heparin has been used in the initial phase. Heparin inhibits the binding of beta 2 glycoprotein I to phospholipid and promotes plasmin mediated inactivation of beta 2
glycoprotein I\textsuperscript{(92)}. In pregnancy heparin acts as anti-inflammatory, by inhibiting complement activation\textsuperscript{(93)}. Heparin is also indicated in acute deep venous thrombosis or pulmonary emboli. Heparin (Low Molecular Weight) acts by binding to the enzyme inhibitors anti thrombin III. Anti thrombin III then inactivates thrombin and other protein involved in blood clotting mainly factor Xa. aPTT measures the effect of heparin. The adverse effect of heparin is thrombocytopenia, hyperkalemia, and osteoporosis. Angioplasty is also useful in acute arterial thrombosis\textsuperscript{(94)}.

**Long term management after thrombotic event:**

Secondary thrombo prophylaxis is taking life-long warfarin. Warfarin inhibits vitamin k dependent factors 2, 7, 9, 10 and protein c and s. Adverse effect of warfarin includes hemorrhage, hemoptysis, warfarin necrosis, osteoporosis by decreasing bone mineral density, and purple toe syndrome.

**WARFARIN NECROSIS:**

Is commonly encountered problem in patients who are on Warfarin. Patients usually presents with petechial, purpuric, bullous and necrotic lesions over breast, thighs, buttock and penis. Mechanism behind warfarin necrosis is warfarin initially inhibits factor VII (half life 1.5-6) and protein c (half life 8
This imbalance in coagulation leads to paradoxical activation of coagulation resulting in hypercoagulable state and thrombosis leading to necrosis.

While using oral anti coagulant international normalized ratio should be maintained between 2.0 and 3.0 to avoid hemorrhagic complications\(^{(95)}\).

\[
\text{INR} = \frac{\text{PT test}}{\text{PT normal}}
\]

It’s a ratio of prothrombin time of test to the prothrombin time of normal. The normal value is 0.8-1.2.

According to the American college of chest physician recommendation treatment with warfarin should be continued for 12 months and consideration of indefinite therapy after initial event\(^{(96)}\).

In case of chronic pulmonary thromboembolism, thromboendarterectomy is indicated\(^{(97)}\).

**Treatment during pregnancy:**

Treatment strategies for women with antiphospholipid antibodies in pregnancy have been designated to suppress the immune system, prevent thrombosis and to improve the placental blood flow by decreasing the thromboxane-to-prostacyclin ratio. Initially high dose prednisolone in combination with low dose aspirin was used.
Treatment of thromboembolism during pregnancy is with either unfractionated or low-molecular weight heparin\(^{(98)}\). Low molecular weight heparin is a derivative of unfractionated heparin, which is safe and effective during pregnancy since it will not cross the placenta. Low molecular weight heparin exerts its anticoagulant activity by activating antithrombin. Table presents the suggested regimens. Treatment is usually initiated during early first trimester. Warfarin is a known teratogen and should be discontinued either prior to conception or by 5\(^{th}\) week of gestation. Heparin is generally stopped during labor and it should be restarted after 12 hours. Postpartum venous thrombosis is treated with intravenous heparin and oral warfarin. Pregnancy loss continue to occur in 20% to 30% of cases even heparin prophylaxis\(^{(99)}\) is given according to current consensus of American college of chest physicians warfarin should be given for at least 6 weeks postpartum but to complete a minimum 6 months course following the initial attack. Trials found that aspirin to be equally beneficial.

Intravenous immunoglobulin’s has also been given during pregnancy to women continued to have poor obstetric outcomes despite treatment with heparin
<table>
<thead>
<tr>
<th>Subcutaneous Heparin Regimens Used in the Treatment of Antiphospholipid Syndrome during Pregnancy</th>
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<tbody>
<tr>
<td><strong>Prophylactic Regimens indications</strong></td>
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<tr>
<td><strong>Unfractionated Heparin</strong></td>
</tr>
<tr>
<td><strong>Low Molecular Weight Heparin</strong></td>
</tr>
<tr>
<td>Adjusted –Dose Anticoagulation Regimens</td>
</tr>
<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
</tr>
<tr>
<td>Recommended in women with antiphospholipid syndrome with a history of thrombotic event(s)</td>
</tr>
<tr>
<td><strong>Unfractioned Heparin</strong></td>
</tr>
<tr>
<td>&gt;7,500 U every 8-12 hours adjusted to maintain the mid-interval heparin levels in the therapeutic range.</td>
</tr>
<tr>
<td><strong>Low Molecular Weight Heparin</strong></td>
</tr>
<tr>
<td>1) Enoxaparin 1 mg / kg every 12 hours or dalteparin 200 U/kg every 12 hours</td>
</tr>
<tr>
<td>2) Intermediate dose (e.g. enoxaparin 40 mg once daily or dalteparin 5,000 once daily until 16 weeks gestation and every 12 hours from 16 weeks gestation onwards.</td>
</tr>
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</table>
Clinical trials found aspirin is found to be equally beneficial in pregnancy loss\(^{(100)}\).

**Treatment of catastrophic antiphospholipid antibody:**

Corticosteroids plays major role in inhibiting cytokine storm and it should be given along anticoagulant. Plasmapheresis, intravenous immunoglobulins and cyclophosphamide also have a role. Plasmapheresis and intravenous immunoglobulin shown efficacy by removing circulating antiphospholipid antibodies. Rituximab in addition to corticosteroids has shown positive results.

Other anticoagulants in use are agents such as dipyridamole, ticlopidine or clopidogrel bisulfate\(^{(101)}\). Have been used for secondary prevention after non-cardio embolic stroke or transient ischemic attack.

**Treatment of stroke:**

Aspirin 325mg is the treatment of choice for stoke with antiphospholipid antibodies\(^{(102)}\).

**Patients with thrombocytopenia and antiphospholipid antibody syndrome:**

Thrombocytopenia does not protect patients with antiphospholipid antibody syndrome from either thrombosis or pregnancy loss. Treatments recommended are prednisolone, denocrine, intravenous immunoglobulin.
After correcting thrombocytopenia careful introduction of warfarin can then be considered.

Splenectomy may be an option for patients with refractory life-threatening thrombocytopenia but recurrences can be seen after splenectomy\(^{(103)}\).

**Treatment of cardiac valvular disease:**

Valvular vegetations occur most frequently on mitral or aortic valve. Corticosteroids should be used in addition to anticoagulants\(^{(104)}\).

**Treatment of thrombi involving central nervous systems:**

Acute therapy usually is with intravenous methyl prednisolone pulse therapy, 1000 mg daily for 3 days, followed by high-dose corticosteroids with or without immunosuppressive\(^{(105)}\) and anticoagulant.

**OTHER THERAPIES:**

**B cell tolerance:**

The ideal prophylactic treatment would be to prevent production of antiphospholipid antibodies, by reintroduction of tolerance\(^{(106)}\). The great benefit of this approach is APS would be inability to induce specific autoantibody tolerance, whereas sparing normal immune function.
**Iv Ig:**

Acts by reducing immunoglobulins in circulation, saturation of IgG transport receptor, anti-idiotypes, interleukin-3 secretion \(^{107}\).

Intravenous Ig is useful in women with pregnancy loss, catastrophic antiphospholipid antibody and patients fail treatment with heparin and aspirin. Intravenous Ig regimens commonly used are 400mg/kg for 5 days monthly or 1g/kg/day for 2 days monthly \(^{108}\).

**High-dose cyclophosphamide, with or without stem-cell rescue:**

Induce tolerance in high dose cyclophosphamide with autologous stem cell rescue can cause long term clinical remission \(^{109}\).

**ANTI TNF:**

tnf-alpha downstreams complement activation \(^{110}\).

**Statins:**

Fluvostatin has been shown to reduce APL induced thrombosis and endothelial cell activation. Inhibits up-regulation of tissue factor by antiphospholipid antibody syndrome \(^{111}\).

**Rituximab:**

B cell depleting monoclonal antibody has shown some promising results. It normalize or reduce antiphospholipid antibody syndrome \(^{112}\).
FUTURE THERAPIES:

The recognition that complement activation is a requirement for antiphospholipid antibody syndrome mediated thrombosis and pregnancy loss leads to biologics that block complement

Peptide therapies:

Peptide that react specifically with anti beta two glycoprotein monoclonal antibodies were identified and found to inhibit endothelial cell activation and expression of adhesion molecule\(^{113}\).

Oral tolerance

Induce oral tolerance to low dose beta 2 glycoprotein \(^{114}\).
MATERIALS AND METHODS:

1. Patients with chronic leg ulcers (fail to heal within a period of 6 weeks) during the period 2010 – 2012.

2. History of all the patients will be recorded and analyzed.

3. Clinical features will be noted.

4. Specific investigations like antinuclear antibody, lupus anticoagulant, anticardiolipin antibody, rheumatoid factor, punch biopsy, doppler, VDRL will be done in all patients.

INCLUSION CRITERIA:

- Both male and females with chronic leg ulcers

- Patients with ulceration connected with connective tissue disorders

- Arterial and venous ulcers
EXCLUSION CRITERIA:

- Acute ulcers
- Traumatic ulcers
- Neuropathic ulcers
- Neoplastic ulcers
- Ulcers due to metabolic disorders
- Drug induced ulcers
- Ulcers due to hematological disease
RESULTS:

- A total of 40 patients were taken up for the study
- Their age ranged from 18 years to 80 years
- 17 patients were female and the remaining 23 males
- The duration of ulcer varied between 2 months to 9 years
- 12 patients were positive once and 4 patients were positive twice
- Of the 4 patients who were twice positive one was primary APLA and 3 were Secondary APLA
- Of the 4 patients twice positive 3 were female and 1 male
- Of the 3 female patients who were twice positive one had pregnancy related complications (Intra uterine death)
- Of the 4 patients who were twice positive one had reactive VDRL(1:8)
- Of the 4 patients one patient doppler study showed arterial thrombus without inflammatory signs.
- Of the 4 patients who were twice positive for antiphospholipid antibody syndrome 2 were positive for ANA.
• Out of the 36 patients who were APLA Negative, 10 had varicose veins, 6 had Vasculitis, 3 had Pyoderma and 17 had chronic ulcer of unknown cause.

• Out of the 8 Patients who were APLA positive once at the time of diagnosis, 2 had varicose veins, 1 had DVT / Varicose Veins, 3 had Vasculitis and 2 had chronic leg ulcer of unknown cause.
RESULTS:

CHART 1: 17 patients were female and the remaining 23 males

CHART 2: 12 patients were positive once and 4 patients were positive twice
CHART 3: Of the 4 patients who were twice positive one was primary APLA and 3 were Secondary APLA.

CHART 4: Of the 4 patients twice positive 3 were female and 1 male
### TABLE 2: NO. OF APLA POSITIVITY

<table>
<thead>
<tr>
<th>NO. OF Patients</th>
<th>APLA POSITIVE</th>
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<tbody>
<tr>
<td></td>
<td>TIME OF DIAGNOSIS</td>
</tr>
<tr>
<td>40</td>
<td>12</td>
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</tbody>
</table>

### TABLE 3: DIAGNOSIS OF LEG ULCER WITH ANTIPHOSPHOLIPID ANTIBODIES POSITIVE ONCE AT THE TIME OF DIAGNOSIS

<table>
<thead>
<tr>
<th>Total No. of Patients</th>
<th>Varicose Veins with ulcer</th>
<th>Varicose veins with DVT</th>
<th>Vasculitis</th>
<th>Chronic Leg ulcer cause unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

### TABLE 4: DIAGNOSIS OF LEG ULCER IN PATIENTS WHO WERE ANTIPHOSPHOLIPID ANTIBODIES NEGATIVE

<table>
<thead>
<tr>
<th>Total No. of Patients</th>
<th>Varicose Veins with ulcer</th>
<th>Vasculitis</th>
<th>Pyoderma gangrenous</th>
<th>Chronic Leg ulcer cause unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>17</td>
</tr>
</tbody>
</table>
DISCUSSION:

Antiphospholipid antibody syndrome is an autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis and fetal loss.

40% of patients have skin manifestations as their primary presenting symptom. Chronic leg ulcer is the second common skin manifestation seen in patients with antiphospholipid antibody syndrome. APLA can cause multi organ involvement and leads to life threatening manifestations such as stroke, myocardial infarction, fetal loss etc. Early detection and treatment can prevent life threatening complications of APLA.

There are not many studies to find out the association of antiphospholipid antibody syndrome and leg ulcer.

So we conducted this study to find out the association between antiphospholipid antibody syndrome and leg ulcers. 40 patients with chronic non healing ulcer are taken up for our study. Out of the 40 patients 4 patients were twice positive for antiphospholipid antibodies 12 weeks apart. 8 patients were once positive for APLA which probably is due to transient rise in APLA in condition like infections and drugs. Usually the titers are lows the raise is transient and if the test is repeated after 12 weeks. It will become Negative.
Alcaraz\textsuperscript{(115)} et al conducted a prospective study on 48 patients with leg ulcers as a manifestation of antiphospholipid syndrome with vascular thrombotic events. Of the 48 patients, out of which 27 were due to venous, 9 arteriovenous and 12 due to arteriolar causes. Circulating anticoagulants were positive in 22 of the 48 patients. 3 patients with venous ulcer had past history of venous thrombosis and 1 patient with arterial ulcer had a past history of arterial thrombosis.

They concluded that antiphospholipid antibodies can be associated with venous ulcers independent of thrombosis history and possible association between arteriolar ulcers and antiphospholipid antibodies requires further large scale studies.

Fink AM\textsuperscript{(116)} et al conducted a study on lupus anticoagulant and venous leg ulceration. They investigated for lupus anticoagulant in 27 patients with venous leg ulcer and compared that data with controls. Of 27 patients, 16 had lupus anticoagulant and only one of the 32 controls was found to have lupus anticoagulant .They concluded that lupus anticoagulant was more frequent in patients with venous leg ulcers than in controls.

Astrid Maria Fink\textsuperscript{(117)} et al conducted a study on lupus anticoagulant in patients with chronic venous insufficiency. They included control group (n=54) and ulcer free group with chronic venous insufficiency
37 patients with CVI were taken for study, 6 were lost on follow-up. 31 patients were divided into two groups, Lupus anticoagulant positive and negative group. Both groups were studied after 4 years. Out of 10 Patients who were positive for lupus anticoagulant 5(50%) had developed leg ulcer within the 4 years of follow-up. Out of 21 patients who were negative for lupus anticoagulant only 2 had developed leg ulcer within the 4 years of follow-up. They concluded that lupus anticoagulant play an important role in the pathogenesis of CVI.

Thelma Larocea Skare\textsuperscript{(118)} conducted a study on leg ulcers and anticardiolipin antibodies. It included 151 patients with leg ulcer and 150 patients in control group. They also obtained clinical data and anticardiolipin antibodies titers. Anticardiolipin antibodies were detected in 7.2% of patients from ulcer group againsts 1.3 % of patients in the control group. They also found that clinical characteristic were not different in patients with and without anticardiolipin antibodies.

In our study, out of 40 patients 4 tested positive for antiphospholipid antibodies and one among the 4 patients had arterial thrombosis on doppler. None of the patients had venous thrombosis.

Vianna JL\textsuperscript{(119)} et al conducted an European multicenter study on 114 patients with antiphospholipid syndrome, out of which 58 had primary
and 56 had secondary antiphospholipid antibody syndrome. They concluded that patients with antiphospholipid antibodies with SLE and primary antiphospholipid antibody syndrome had similar clinical profiles but heart valve disease, hemolytic anemia, low c4 levels and neutropenia were more common in patients with secondary antiphospholipid antibody syndrome. In our study out of 4 patients who showed antiphospholipid antibody positivity 3 were secondary antiphospholipid antibodies syndrome. All the 3 patients had anemia and one patient had thrombocytopenia and one patient had intrauterine death.

Weber M\textsuperscript{(120)} conducted a study on family history of patients with primary or secondary antiphospholipid syndrome. It was a retrospective study on 108 patients with antiphospholipid antibody syndrome managed during the ten year study period. Out of 108 patients 39 had primary and 69 had secondary antiphospholipid antibody syndrome. He found that 12 primary and 19 secondary patients had 1 or more relatives with evidence of at least one clinical feature of APLA such as thrombosis or recurrent fetal loss. He concluded that a positive family history is common in patients with primary and secondary APLA. The percentage of a positive family history for autoimmune disease tends to be higher in patients with secondary APLA than
in those with primary APLA. In our study, none of our APLA positive patients had family history of autoimmune disease.

Lima F(121) et al conducted a study of sixty pregnancies in patients with the antiphospholipid syndrome. 60 pregnancies in 47 antiphospholipid antibody syndrome patients (11 primary and 36 secondary) were followed in a multidisciplinary clinic. Patients testing APLA positive and having history of recurrent miscarriages were treated with low-dose aspirin daily. Patient with APS and previous history of thrombotic events were treated with low molecular weight heparin and low-dose aspirin daily. They concluded that live birth rate increased from 19% of previous untreated pregnancies to 70% despite high incidence of fetal and obstetric complications like pre-eclampsia, prematurity, fetal distress and intrauterine growth retardation.

Rai RS(122) et al conducted a study on high prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. They studied the outcome of 20 pregnancies in women with antiphospholipid antibodies and history of recurrent miscarriage. Comparison was made with a cohort of 100 consecutive women with recurrent miscarriage in whom no underlying cause to account for their pregnancy losses was found. Of the 20 women with antiphospholipid antibody, 18(90%) miscarried compared to 34 of the 100 women(34%)with normal investigations.
They found that majority of miscarriages in women with antiphospholipid antibodies occurred in the first trimester and the first trimester loss of embryonic pregnancies is the most common type of miscarriage in women with antiphospholipid antibodies. In our study of the 4 positives, 3 were female; of the 3 one patient had history of two intra uterine death by 3rd and 2nd trimester.

Camille Frances\textsuperscript{123} et al conducted a study on dermatologic manifestation of the antiphospholipid syndrome. 200 patients with primary and secondary antiphospholipid antibody syndrome were included in the study and livedo reticularis was the most frequent manifestation observed in 25.5% of patients. He concluded that livedo reticularis is the commonest dermatological manifestation and it is significantly associated with the arterial subset of antiphospholipid antibody syndrome. In our study none of the 4 patients who had leg ulcer with positive antiphospholipid antibodies had livedo reticularis.

There are also studies showing increased frequency of antiphospholipid antibodies and leg ulcer in sickle cell anemia. In a study conducted by Edeghonghon E Olayemi\textsuperscript{124} et al, 33 patients with chronic leg ulcer and 33 patients without chronic leg ulcer were screened for the presence of lupus anticoagulant. They concluded that sickle cell anemia with chronic leg

 ulcer may be more likely to develop lupus anticoagulant, and this may be related to the degree of hemolysis.

There are many case reports of antiphospholipid antibody syndrome with different clinical presentations. In one report 72 year old female presented with bilateral necrotic ulcers on lower limb for 5 months with recurrent thromboembolism. Biopsy was done which showed multiple venous and arterial thromboses without signs of inflammation. Lab investigations revealed circulating anticardiolipin, lupus anticoagulant and antinuclear antibodies. After treatment with anticoagulant patient’s condition improved.

There are also reports mentioning the cutaneous ulcers of antiphospholipid antibody syndrome resembling pyoderma gangrenosum.

There are many case reports showing increased incidence of APLA antibodies seen in patients with klinefelter syndrome. These reports suggest that when patients with klinefelter syndrome present with recurrent thrombosis or additional features of autoimmune disease, patient should be subjected to tests for antiphospholipid antibodies.
Conclusion

In our study 10% of the patients with leg ulcers had antiphospholipid antibodies. These antibodies are associated with considerable mortality and morbidity and so early detection and treatment is important to prevent life threatening complications like thrombosis. Antiphospholipid antibody is important in the evaluation of patients with chronic non healing ulcer.
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PROFORMA FOR ANTIPHOSPHOLIPID ANTIBODY SYNDROME:

Name: Age: Sex:

IP.No: Social Status: Occupation:

Address:

Chief Complaints:

Ulcer - Y/N Duration:

Painful - Y/N

History of Presenting Illness:

Duration –
Mode of onset – Acute/Gradual/
Pain – Nature of pain –
   Site of pain –
   Time of onset –
Site of Ulcer:

Discharge:

Progress of Ulcer:

Fever:

Trauma:

Presence of any other ulcer:

Impairment of functions:

Recurrence of ulcer:

Loss of body weight:
PAST HISTORY:

Hypertension-
Diabetes-
Atopy-
Abortions-
Preterm births -

Personal History: menstrual history

Family History:

General Examination: General Condition – Good/Fair/Bad
Build and Nutritional status:
Hydration:
Pallor: Cyanosis: Clubbing:
Pedal Edema: Generalised Lymphadenopathy:
Icterus: Pulse: BP: mm of Hg Temp:

Local Examination:
Inspection: Site-
Size- Shape- floor -
Edges - margins - Discharge - surrounding skin-
Number- Pulsations- Fixity-

Palpation:
Temperature: Tenderness:
Size: Shape: Extent:
Edges : margins: base:
Regional Lymph nodes:

Peripheral Pulses:

Clinical Diagnosis:

INVESTIGATIONS:
HB- RBS-
TC- BL.UREA-
DC- SR.CREAT-
ESR- SR.ELECTROLYTES- NA+ - CL- K+
URINE- ALBUMIN-
SUGAR-
DEPOSITS-
BL.GROUP:

Antinuclear antibody-

Lupus anticoagulant –

Anticardiolipin antibody-

Rheumatoid factor -

VDRL-

Punch Biopsy:

Doppler:
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<td>PG</td>
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<td>PG</td>
<td>98943-58760</td>
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<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>