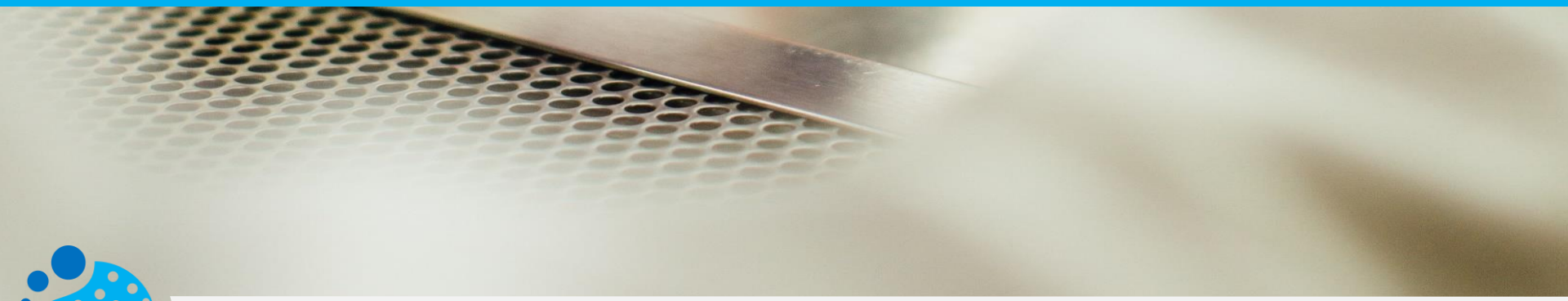
Antiphospholipid Syndrome



The antiphospholipid syndrome is an autoimmune disease that is characterized clinically by vascular thrombosis and pregnancy morbidity, and serologically by the presence of Antiphospholipid Antibodies

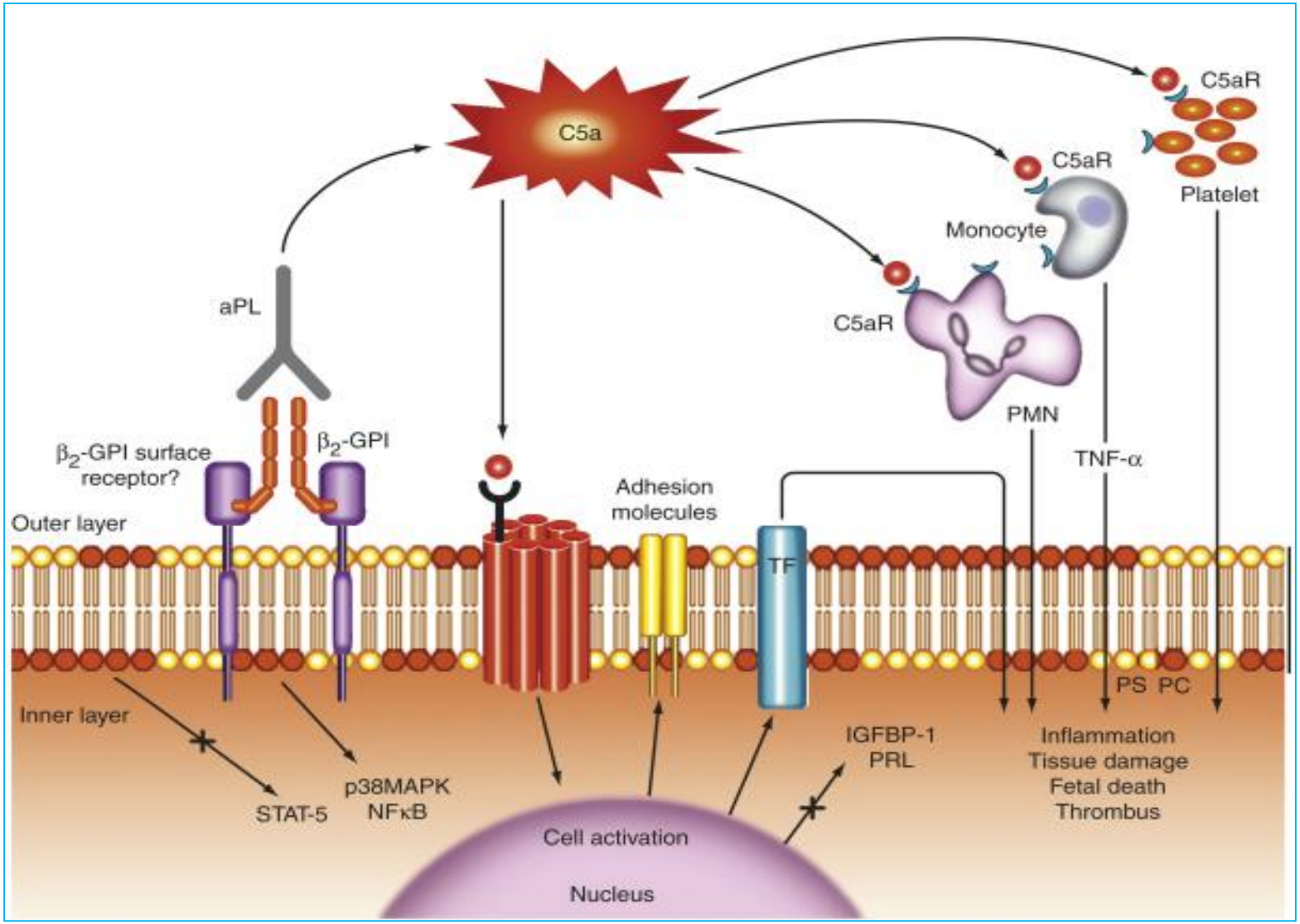
Epidemiology

- 10% of normal population have transient low-titer anticardiolipin; 1% have moderate-high titers
- 50% of APS patients have SLE (defined as secondary APS)
- Up to 40% of SLE patients have positive aPL tests and 10-20% have APS
- Asymptomatic aPL-positive patients have a 0% to 4% annual risk of thrombosis
- 14% of patients with recurrent venous thromboembolic disease have aPLs

Etiology

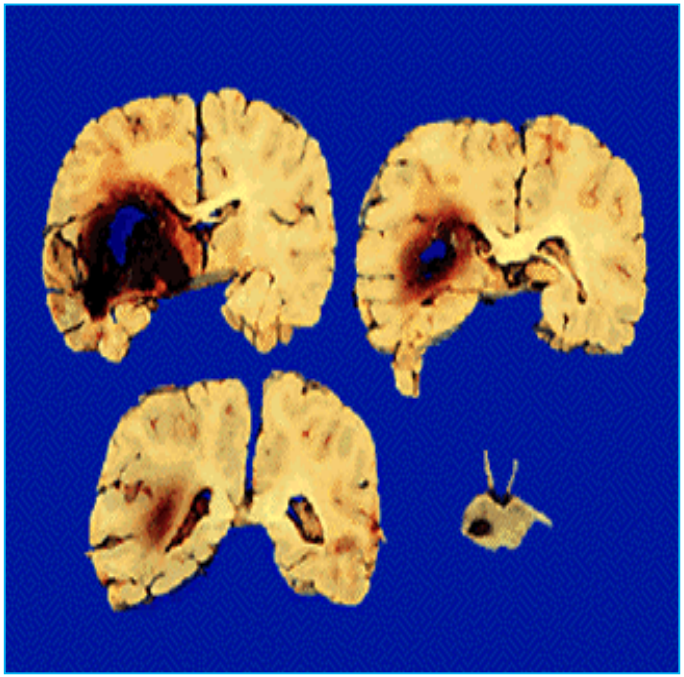
- The main Ag is ß2GPI a physiologic phospholipid-binding plasma protein
- ß2GPI binds to phosphatidylserine on activated or apoptotic cell membranes and function in the elimination of apoptotic cells, removal of oxidized lipids, and is a natural anticoagulant
- Drugs (chlorpromazine, procainamide, quinidine, and phenytoin) and malignancies (lymphoproliferatives) can also induce non-autoimmune aPLs

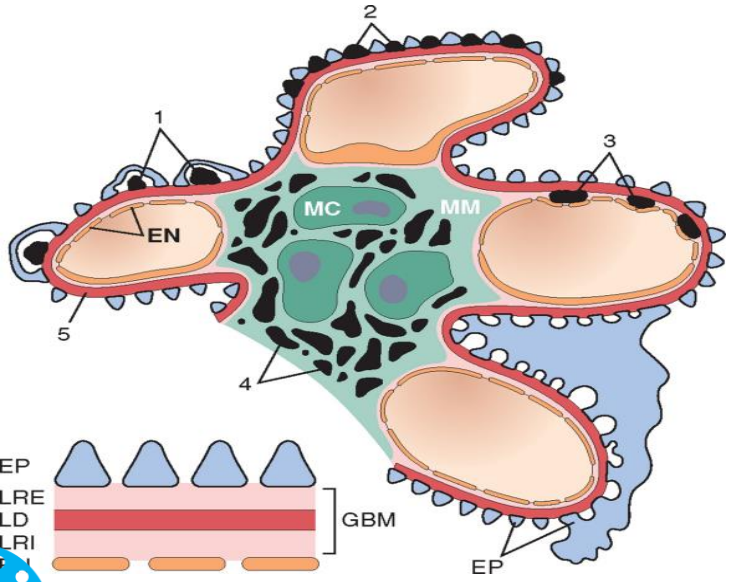
Pathogenesis

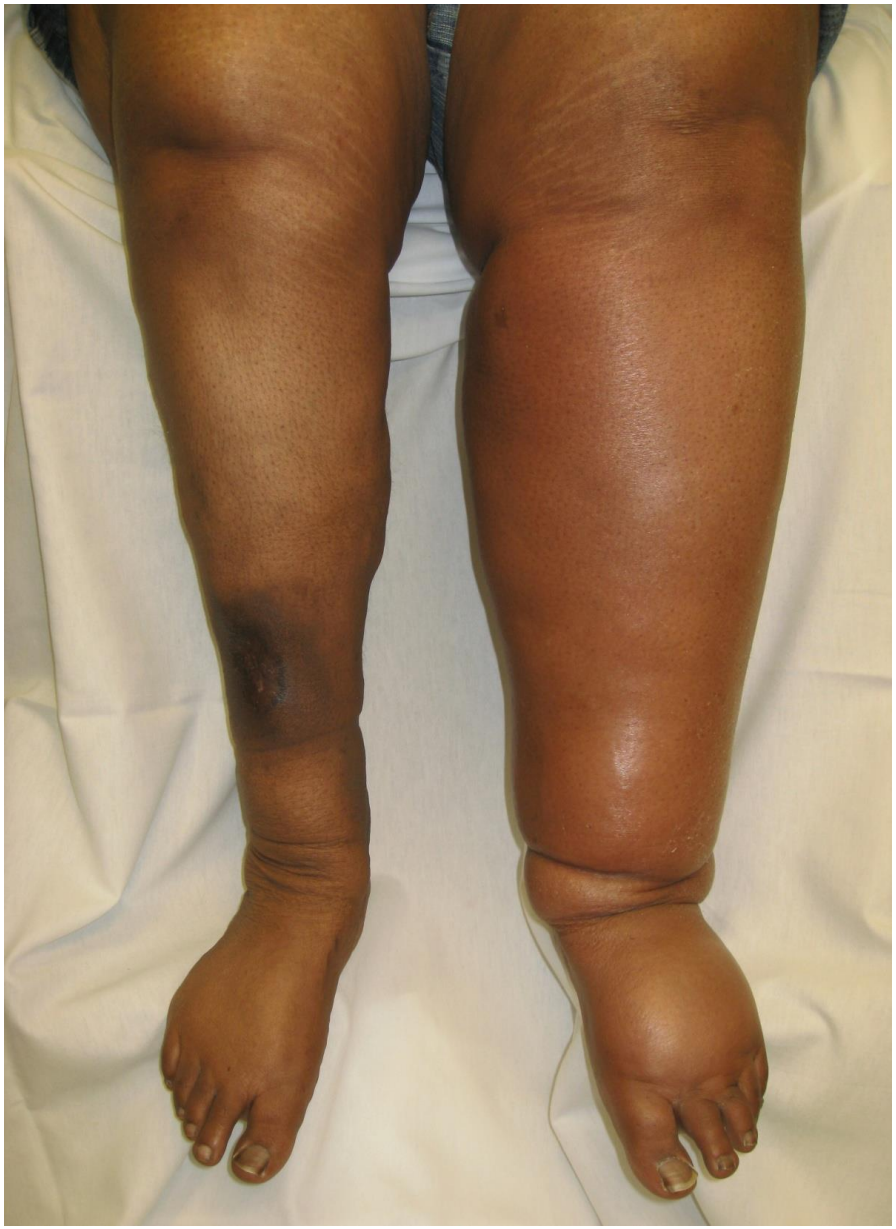


Manifestations : Thrombosis

- Venous and/or arterial occlusion may occur in any organ
- Thromboses may be sever, recurrent, and occur in unusual sites and in young peoples
- DVT and stroke are the most common clinical manifestations of APS
- Severe HTN, renal failure and proteinuria without casts may occur due to renal microangiopathy, glomerular capillary injury, and thrombosis of renal vessels





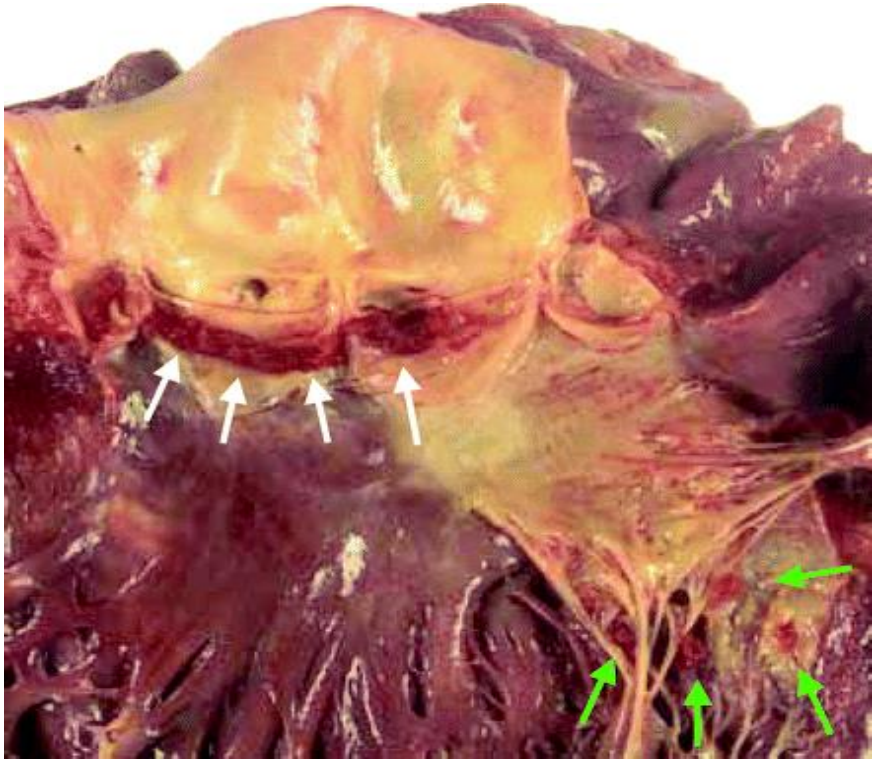


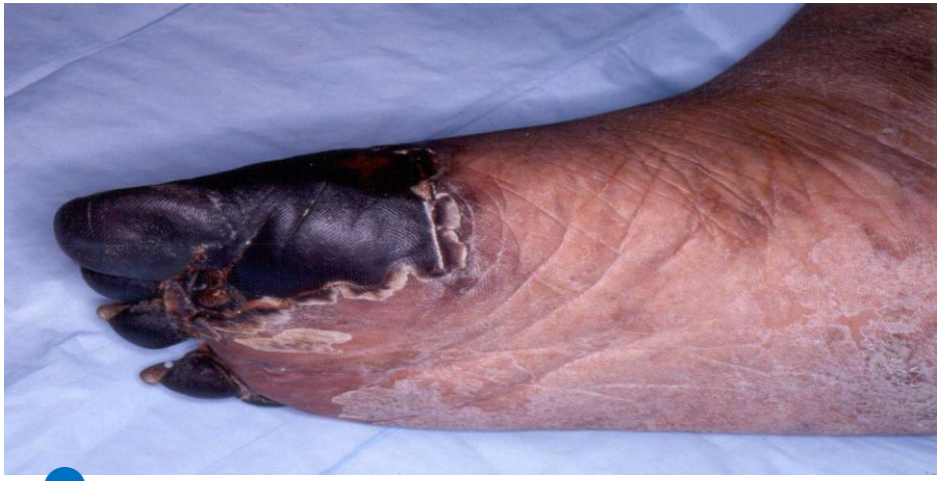
Pregnancy Complications

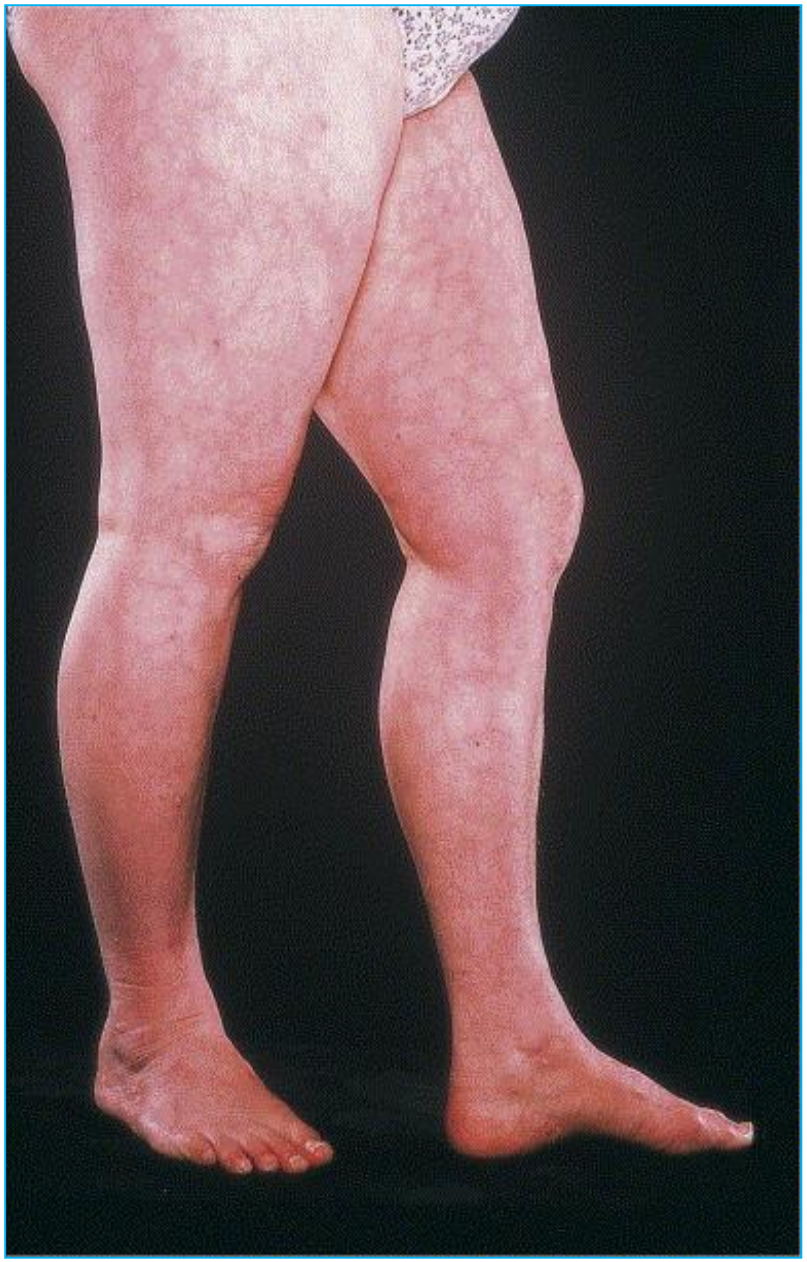
- Losses in patients with aPLs typically occur after 10 weeks.
- Fetal growth slows and amniotic fluid volume decreases in second trimester
- Severe, early preeclampsia or HELLP syndrome may develop
- Prior late pregnancy losses predict future losses

Non-thrombotic Manifestations

- Livedo reticularis is common but is not specific for APS
- Cardiac valve disease (vegetations, thickening), is a late manifestation
- Accelerated atherosclerosis is not evident in recent studies
- Leg ulcers may develop







Miscellaneous Manifestations

- Pulmonary hypertension may develop due to recurrent pulmonary embolism or small vessel thrombosis
- Nonfocal neurologic symptoms are lack of concentration, forgetfulness, and dizzy spells
- Multiple small, hyperintense lesions seen on MRI in the periventricular do not correlate well with clinical symptoms
- Antiprothrombin antibodies may cause hemorrhage during lupus anticoagulant hypoprothrombinemia syndrome

Catastrophic Antiphospholipid Syndrome (Caps)

- Multiple thromboses of medium and small arteries occurring over a period of days
- Stroke, cardiac, hepatic, adrenal, renal, intestinal infarction; acute adrenal failure and peripheral gangrene can occur
- Thrombocytopenia is moderate; erythrocytes are less fragmented than in the HUS or TTP, and fibrin splits are not strikingly elevated
- Tissue biopsies show noninflammatory vascular occlusion

Laboratory Tests

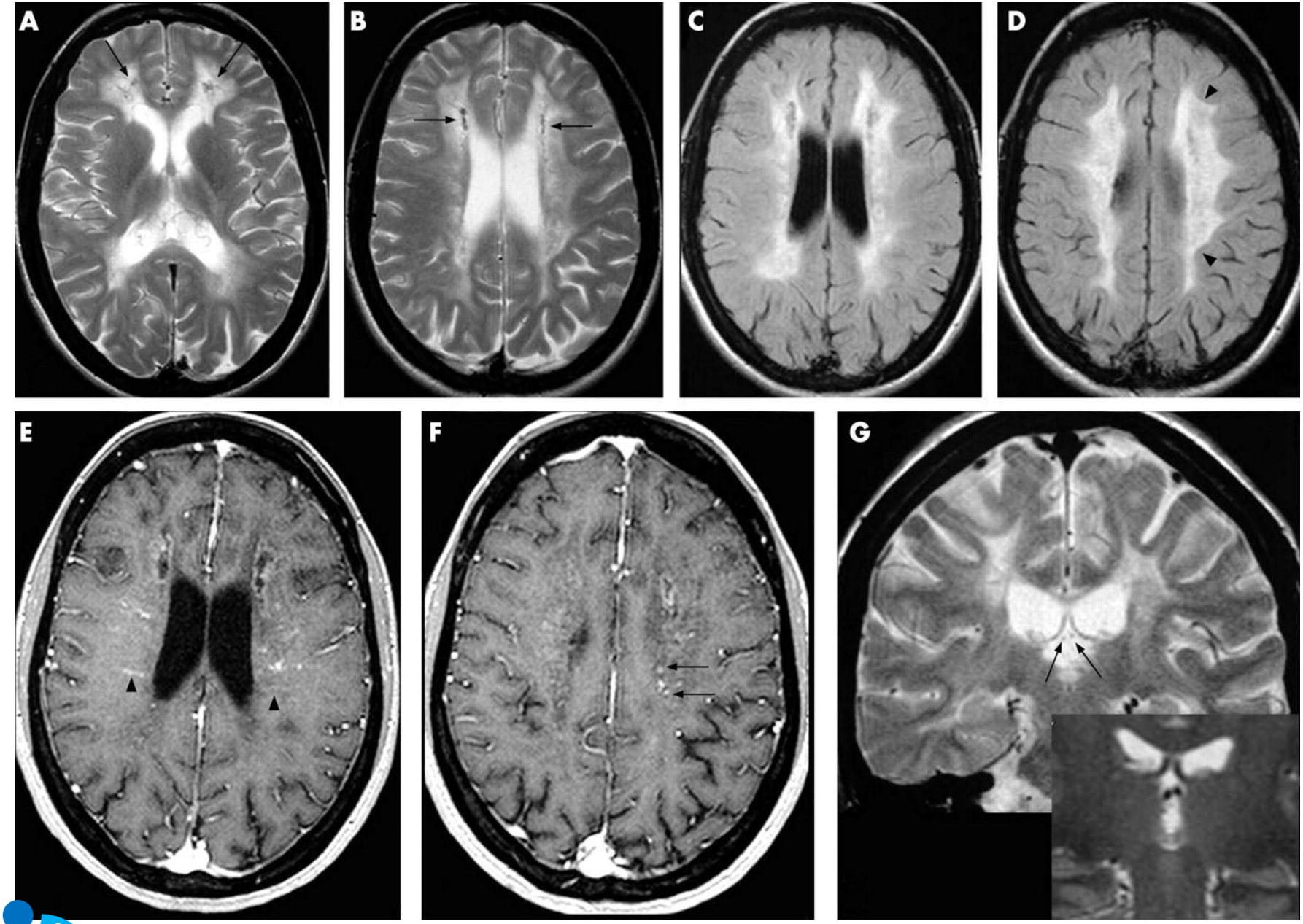
- Repeatable positive LA test or
  - A moderate- to high-titer aCL IgG
  - or IgM test is required
- IgA aCL and (IgG, IgM, or IgA anti-ß2GPI) are helpful when LA and aCL tests are negative
- LA test is more specific but less sensitive predictor of thromboses

Laboratory Tests

- ANA and anti-DNA antibodies occur in 45% of patients with primary APS
- Hypocomplementemia, erythrocyte casts, and pyuria imply lupus nephritis rather APS
- ESR, Hb, and WBC count are normal in uncomplicated primary APS, except during acute thrombosis

Imaging

- MRI shows CVA and other infarctions
- Multiple small, hyperintense white-matter lesions are common and may not be infarcts
- Occlusions usually occur in vessels below the angiographic resolution
- Echocardiography or cardiac MRI may show Libman-Sacks endocarditis and thrombi



Pathology

- Noninflammatory occlusion of all caliber arteries and veins, acute and chronic endothelial injury is noted
- Uteroplacental insufficiency may be due to inflammation rather than thrombosis or spiral artery vasculopathy
- Necrotizing vasculitis suggests concomitant SLE

Diagnosis : Clinical Criteria

1. **Vascular thrombosis :** A clinical episodes of arterial, venous, or small vessel thrombosis in any organ
2. **Pregnancy morbidity :**
   a) An unexplained fetal deaths beyond the 10th week of gestation, or
   b) One premature birth before the 34th week because of eclampsia, severe preeclampsia or placental insufficiency or
   c) Three unexplained consecutive abortions before the 10th week (not with anatomic, hormonal or chromosomal causes)

Diagnosis: Lab Criteria

1. LA on two or more occasions at least 12 weeks apart
2. aCL of immunoglobulin Ig G or IgM in medium or high titer, on two or more occasions at least 12 weeks apart, by ELISA
3. Anti– ß2GPI antibody of IgG or IgM on two or more occasions at least 12 weeks apart, measured by ELISA

Note: Definite APS is present if at least one of the clinical and one of the lab criteria are met

Diagnosis : Suggesting Features

Clinical:

- **Livedoreticularis**
- **Thrombocytopenia** (usually 50,000-100,000 /mm3)
- **Autoimmune hemolytic anemia**
- **Cardiac valve disease**
- **Multiple sclerosis–like syndrome**, **chorea**, or other **myelopathy**

Laboratory:

- IgA *aCL* antibody
- IgA *Anti– ß2GPI*

Diagnosis : CAPS

1. Involvement of three or more organs or tissues
2. Development of in less than 1 week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue
4. Laboratory confirmation of the presence of aPL (LA or aCL or Anti– ß2GPI)

Definite Catastrophic APS: All 4 criteria

Treatment : Vascular dis.

- Acute thrombosis is treated as usual patients
- Moderate intensity (INR 2 to 3) and high-intensity warfarin (INR 3 to 4) are equally protective
- Arterial thrombosis who are at high risk for recurrence require high-intensity anticoagulation
- Aspirin is an option for elderly with a single low-titer aCL and one stroke
- Positive LA may cause the INR to be unreliable, if so, anti–factor Xa activity testing is helpful

Treatment : Vascular dis.

- Aspirin, HCQ, statins , IVIG, and plasmapheresis have been used in refractory cases
- GCs have are used for rheumatic symptoms, High doses used empirically in severe thrombocytopenia, hemolytic anemia, and CAPS
- Discontinuing anticoagulation in highly selected patients when the triggers are eliminated and full remission of antibody observed

Treatment: Pregnancy Morbidity

- Unfractionated or LMWH is used. But lower risk of thrombocytopenia and osteoporosis with the later
- Prior fetal losses are treated with prophylactic doses, prior thromboses must be fully anticoagulated.
- In women with prior thrombosis, warfarin is changed to heparin before conception, or at the first missed menstruation

Treatment: Pregnancy Morbidity

- Anticoagulation is continued for 6 to 12 weeks post partum
- Conversion from heparin to warfarin is done after the first or second postpartum week
- Breastfeeding is permissible with both heparin and warfarin.

Treatment: Asymptomatic Individuals

- The probability to develop APS is low
- Elimination of reversible risk factors and prophylaxis during surgical procedures, are crucial
- Drugs that promote thrombosis (estrogen, etc.) may not be safe

Treatment: Ambiguous Events

- Dizziness, visual disturbance, very early pregnancy loss are treated with ASA, HCQ, or both
- In livedo reticularis, thrombocytopenia, leg ulcers, microangiopathy, or valvulopathy the efficacy of anticoagulation is unknown
- Rituximab can be effective for refractory thrombocytopenia and skin ulcers

Treatment Review

Asymptomatic	→	**No treatment**
Venous thrombosis	→	**Warfarin INR 2.5 indefinitely**
Arterial thrombosis	→	**Warfarin INR 2.5 indefinitely**
Recurrent thrombosis	→	**Warfarin INR 3 to 4 & low dose aspirin**

Treatment Review

First pregnancy	→	No treatment
Single pregnancy loss at <10 weeks	→	No treatment
≥1 Fetal or ≥3 embryonic loss	→	Prophylactic heparin + low-dose ASA, discontinue 6-12 wk postpartum
Thrombosis regardless of pregnancy Hx	→	Therapeutic heparin or low-dose ASA throughout pregnancy, warfarin postpartum

Treatment Review

Valve nodules or deformity	→	No known effective treatment; full anticoagulation if emboli or intracardiac thrombi
Thrombocytopenia >50,000/mm3	→	No treatment
Thrombocytopenia <50,000/mm3	→	Prednisone, IVIG
Catastrophic APS	→	Anticoagulation + corticosteroids + IVIG or plasmapheresis

Prognosis

- Prognostic factors are: pulmonary hypertension, neurologic involvement, myocardial ischemia, nephropathy, gangrene of extremities, and CAPS
- Renal failure due to microangiopathy is rare
- Thrombosis may cause loss of a transplanted kidney or other organ
- Valvulopathy may need valve replacement
- Perioperative complications may occur despite prophylaxis
- Mortality is 50% in CAPS