Review Article

Antiphospholipid syndrome in dermatology: An update

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ABSTRACT

Antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies, recurrent thrombosis, and fetal loss. Antiphospholipid antibodies are a family of autoantibodies that recognize various combinations of phospholipids, phospholipid-binding proteins, or both. APS can occur in the absence of underlying or associated disease (primary APS) or in combination with other diseases (secondary APS). The exact pathogenic mechanism by which these antibodies cause thrombosis is not known; however, several hypotheses, such as activation of platelet and endothelial cells and interference with the coagulation system, have been proposed. Diagnosis is based on the presence of at least one clinical and laboratory criterion each, according to International Consensus Statement on preliminary classification criteria. However, APS can be diagnosed in individuals even in the absence of some of the classification criteria. Clinical manifestations involve different organs and systems such as the blood vessels, central nervous system, skin, kidneys, gastrointestinal tract, heart, and placenta. The unifying mechanism of all these manifestations is thrombosis, either arterial or venous. Skin manifestations are varied and although not included in the diagnostic criteria, may be the presenting feature of this syndrome. Therefore all dermatologists should investigate the possibility of APS when cutaneous findings are related to venous or arterial thrombosis. The risk of thrombosis cannot be predicted, and therefore treatment is not initiated until a thrombotic event occurs. Indefinite anticoagulation is prescribed once a thrombotic event occurs. Prognosis depends on the severity of the clinical manifestations and so, knowledge of the presentation of this disease is important for early detection and prompt treatment to prevent life-threatening consequences of this catastrophic disease process.

Key words: Antiphospholipid syndrome, antiphospholipid antibodies, recurrent thrombosis, fetal loss

INTRODUCTION

Antiphospholipid antibodies (aPL) constitute a heterogeneous group of autoantibodies that share the ability to bind phospholipid alone, protein-phospholipid complexes, or phospholipid binding proteins. Antiphospholipid Syndrome (APS) is the association of aPL with hypercoagulability resulting in arterial and/or venous thrombosis, and pregnancy morbidity/obstetric complications. These antibodies include lupus anticoagulant antibodies, anticardiolpin antibodies (aCL), antibodies against -β_2-glycoprotein I antibodies (anti-2GPI). The lupus anticoagulant antibodies are responsible for prolongation of the activated partial thromboplastin time *in vitro* but a hypercoagulable state *in vivo*.

This syndrome is termed as primary (primary APS) when it occurs in the absence of underlying or associated diseases; Secondary APS is associated with autoimmune diseases such as systemic lupus erythematosus (SLE).[1] A wide variety of conditions associated with aPL are listed in Table 1.

Antiphospholipid antibodies can also occur incidentally in healthy individuals and as a result, aPLs are considered clinically significant only when present in APS.[2] Clinical features can vary widely and can involve

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Table 1: Conditions associated with antiphospholipid antibodies

Common autoimmune or rheumatic diseases with aPL	SLE, Sjögren syndrome, Rheumatoid arthritis, Autoimmune thrombocytopenic purpura, Autoimmune hemolytic anemia, Psoriatic arthritis, Systemic sclerosis, Mixed connective-tissue disease, Polymyalgia rheumatica, giant cell arteritis, Behçet syndrome.
Infections	Syphilis, Hepatitis C infection, HIV infection, Human T-cell lymphotrophic virus type 1 infection, Malaria, Bacterial septicemia
Drugs	Cardiac - Procainamide, quinidine, propranolol, hydralazine. Neuroleptic or psychiatric - Phenytoin, chlorpromazine. Other - Interferon alfa, quinine, amoxicillin

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 features as the major complaint.[3] 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.

HISTORY

The first aPL, a complement fixing antibody that reacted with extracts from bovine hearts, was detected in patients with syphilis in 1906.[4] The relevant antigen was later identified as cardiolipin, a mitochondrial phospholipid.[5] This observation became the basis for the Venereal Disease Research Laboratory (VDRL) test for syphilis, which is currently used. It was later established that many patients with SLE had positive test for VDRL without any other evidence for syphilis.[6]

In 1983, Harris and co-workers described a radioimmunoassay for the estimation of anticardiolipin antibodies (aCL),[7] and two years later they developed the first enzyme-linked immunosorbent assay (ELISA) for the quantitative detection of anticardiolipin antibodies.[8] These developments led to a renewed interest in aPL, which in turn led to the description, by Hughes and his colleagues in 1986, of the anticardiolipin syndrome.[9] A year later, Harris *et al.* coined the term "antiphospholipid syndrome".[10] Although Hughes *et al.* had recognized the features of APS in "non-lupus" patients,[11] it was Asherson who introduced the term "primary Anti Phospholipid Syndrome" to describe patients with APS without an underlying disorder, as opposed to secondary APS, which occurs in the context of another autoimmune disorder.[12]

In the early 1990s, two groups discovered that some aCL require the presence of the plasma phospholipids-binding protein β_2-glycoprotein I (β2GPI) to bind to cardiolipin.[12,13] This requirement is a feature of aCL from patients with SLE or the APS but not from patient with syphilis or other infectious diseases.[12-14] The demonstration that aCL are directed against a phospholipid-binding protein rather than phospholipids led to the discovery that some autoantibodies bind directly to β2GPI in the absence of phospholipids.[12,15] This has resulted in a change of focus from phospholipids to phospholipids binding proteins.[16]

PATHOGENESIS

Phospholipids are a class of polar lipids composed of a phosphate moiety and one or more fatty acid molecules produced in all types of cell in the body. Phospholipids found in the tissues are either anionic (phosphotidyl serine, phosphotidyl ionositol, phosphatidic acid and cardiolipin) or neutral (phosphotidyl choline and phosphotidyl ethanolamine).[17]

Antiphospholipid antibodies were initially thought to target anionic phospholipids. But various evidences suggest aPLs are directed against a variety of phospholipid-binding proteins such as β 2GPI,[18] prothrombin,[19] protein C, and protein S[20] immobilized on anionic phospholipid membranes. The link between aPL, APS and thrombosis has not been conclusively elucidated. Several hypotheses have been proposed to explain the cellular and molecular mechanisms by which antiphospholipid antibodies promote thrombosis.

Interference with coagulation cascade

Phospholipids are critical at several points in the extrinsic, intrinsic, and common pathways of the coagulation cascade [Figure 1]. Phospholipids are necessary for activation of factor X in the intrinsic pathway, activation of factors IX and X in the extrinsic pathway and conversion of prothrombin to thrombin in

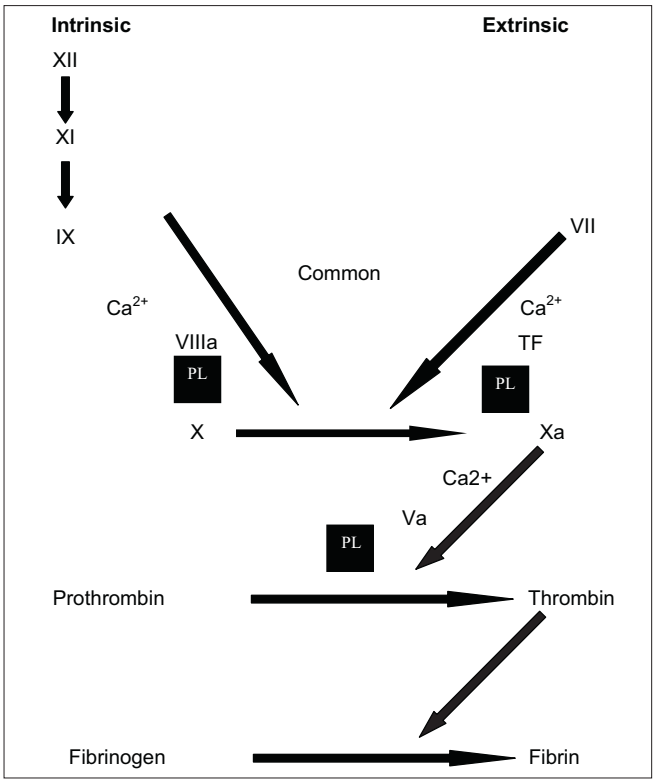

Figure 1: Coagulation Cascade and Phospholipids. Figure shows the extrinsic and intrinsic pathways of coagulation and the sites of phospholipids requirement. The various clotting factors are mentioned in the Roman numbers. PL – Phospholipids, TF - tissue factor, Ca – Calcium

the final or common pathway. The aPL interfere with or modulate the function of phospholipid-binding proteins involved in the regulation of coagulation leading to hypercoagulable state by the following mechanisms:

a. The interaction of aCL with β2GPI bound to phospholipid inhibits protein C, protein S, which are natural anticoagulants.[21]
b. Antiphospholipid antibodies bind to thrombin activated platelets, inhibiting thrombin-mediated endothelial cell prostacyclin release or inhibiting protein C activation.[22]
c. Autoantibodies to a variety of endothelial cell surface proteins including thrombomodulin, heparin sulfate, and heparin sulfate proteoglycan have been described. IgG aPLs that react with heparin sulfate have been shown to inhibit the formation of anti-thrombin III complexes that could contribute to vascular thrombosis.[23]
d. Finally, antibodies against platelet-activating factor in patients with autoimmune diseases and APS have been identified.[24]

Activation of endothelial cells

Antiphospholipid antibodies recognize β2GPI bound to resting endothelial cells, although the basis for the interaction of β2GPI with viable endothelial cells remain unclear.[25] Binding of antiphospholipid antibodies induces activation of endothelial cells, as assessed by up-regulation of the expression of adhesion molecules, the secretion of cytokines and the metabolism of prostacyclins resulting in hypercoagulation.[26]

A second theory focuses on oxidant-mediated injury of the vascular endothelium. Oxidized low-density lipoprotein (LDL), a major contributor to atherosclerosis, is taken up by macrophages, leading to macrophage activation and subsequent damage to endothelial cells.[27] Autoantibodies to oxidized LDL occur in association with aCL, and some anticardiolipin antibodies cross-react with oxidized LDL.[28] Moreover, anticardiolipin antibodies bind to oxidized cardiolipin, suggesting that anticardiolipin antibodies recognize oxidized phospholipids, phospholipid-binding proteins, or both,[29] thus contributing to hypercoagulation.

DETECTION OF ANTIPHOSPHOLIPID ANTIBODIES

The most commonly detected subgroups of aPL are lupus anticoagulant antibodies, aCL and anti-β2GPI.

Division into these subgroups is broadly based on the method of detection. Lupus anticoagulant antibodies are identified by coagulation assays in which they prolong clotting times. In contrast, aCL and anti-β2GPI are detected by immunoassays that measure immunologic reactivity to phospholipids or phospholipids-binding protein (cardiolipin and β2GPI, respectively)[30] as described in Table 2. In general, lupus anticoagulant antibodies are more specific for APS and aCLs are more sensitive.[31] The specificity of aCL for APS increases with titer and is higher for IgG than IgM isotope.

CLASSIFICATION CRITERIA FOR DETECTION OF ANTIPHOSPOLIPID SYNDROME

In 1999 an International Workshop issued the first Consensus Statement on preliminary classification criteria for definite APS.[32] The classification criteria were revised in 2006 at the Eleventh International Congress on aPLs in Sydney, Australia. The clinical and laboratory criteria for APS were updated [33] and definite APS was the presence of at least one of the clinical and one of the laboratory criteria as outlined in Table 3.

Table 2: Detection of antiphospholipid antibodies[30]

Lupus anticoagulant antibodies
Detection by clotting assays
The first step is prolongation of coagulation in at least one phospholipid dependent *in vitro* coagulation assay with the use of platelet-poor plasma.
These assays evaluate as follows:
a) The extrinsic coagulation pathway (dilute prothrombin time) The intrinsic coagulation pathway (activated partial-thromboplastin time, dilute activated partial –thromboplastin time, and kaolin clotting time) The final common coagulation pathway (dilute Rusell's viper-venom time, Taipan venom time, and textarin and Ecarin times)
b) The second step is failure to correct the prolonged coagulation time by mixing the patients plasma with normal plasma.
c) The third step is confirmation of the presence of lupus anticoagulant antibodies by shortening or correction of the prolonged coagulation time after the addition of excess phospholipid or platelets that have been frozen and then thawed.
d) The fourth step is ruling out other coagulopathies with the use of specific factor assays if the confirmatory test is negative or if a specific factor inhibitor is suspected.
Detection of antiphospholipid antibodies by immunoassays
Antibodies against cardiolipin (aCL)detected by ELISA
Antibodies against β2GPI (anti-β2GPI) detected by ELISA
Antibodies against Prothrombin (aPT) detected by ELISA
Antibodies against phospholipids other than cardiolipin (e.g., phosphotidyl serine, phosphotidyl ethanolamine) detected by ELISA.
Antibodies against phospholipids/ cholesterol complexes detected as biological false positive test for syphilis (BFP) and Venereal Disease Research Laboratory tests (VDRL)
Antibodies against phospholipids-binding plasma proteins (e.g., annexin) detected by ELISA

Table 3: Classification criteria for detection of APS

Clinical criteria
Vascular thrombosis: One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ confirmed by objectively validated criteria (imaging or Doppler studies or histopathology), with the exception of superficial venous thrombosis
Pregnancy morbidity:
(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
(b) One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia or severe placental insufficiency, or
(c) Three 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
Laboratory criteria
1. Lupus anticoagulant present in plasma, on two or more occasions, at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Subcommittee on Lupus Anticoagulants / Antiphospholipid Antibodies)
2. aCL of IgG and/or IgM isotype in serum plasma, present in medium or high titer on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-β2GPI of IgG and/or IgM isotype in serum or plasma (titer >99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA according to recommended procedures

GENETIC PREDISPOSITION

There is a familial association and relatives of persons with known APS are more likely to have aPL antibodies. Various studies suggest a familial occurrence of aCL and Lupus anticoagulant, with or without clinical evidence of APS.[34] This familial tendency could be genetically determined, because APS, aCL, and lupus anticoagulant occur in families carrying haplotypes which contain HLA-DR4, -DR7, and -DRw53. . HLA-DR4 seems to be more important in Anglo-Saxons, whereas DR7 in populations of Latin origin.[34]

EPIDEMIOLOGY

Several studies have been conducted to establish the prevalence of aPL in cohorts of healthy subjects. The rationale behind these studies is that knowing the prevalence of aPL in healthy persons is necessary to establish associations between aPL and different clinical manifestations: most of the studies report a frequency of elevated aPL between 1% and 5%.[35] Most aPL in apparently healthy individuals are low titer and transient. The presence of aPL in pregnant women has been associated with pregnancy morbidity and the prevalence of aPL in healthy pregnant women has been reported to be as high as 5.3%.[36]

The elderly have many autoantibodies which increase with age and most studies report a higher prevalence of aPL in the elderly than in younger adults.[37]

Among patients with SLE, the prevalence of aPL is much higher, ranging from 12 to 30% for aCL[38,39] and 15 to 34% for lupus anticoagulant antibodies.[39] In contrast, the APS may develop in 50 to 70 % of patients with both SLE and aPL after 20 years of follow-up.[35]

CLINICAL MANIFESTATIONS OF ANTIPHOSPOLIPID SYNDROME

The clinical manifestations of APS involve different organs and systems, such as blood vessels, central nervous system, skin, kidneys, gastrointestinal tract, heart and placenta. The unifying mechanism of all these manifestations is thrombosis, either arterial or venous.

The spectrum of clinical manifestations that are associated with aPL is extensive. Those included in the classification criteria are outlined in Table 3. However, some clinical manifestations, such as heart valve disease, livedo reticularis, thrombocytopenia, APS nephropathy and neurological manifestations, have not been included in the criteria.[33]

The literature on the clinical manifestations of APS is vast and includes a number of case reports, but there are two reports on large series of patients with APS, which provide reliable information as to the relative frequency of the different clinical manifestations of this syndrome.[40,41] In a multicenter study, 53.1% of patients had primary APS, while 36.2% had SLE with secondary APS. The most frequently presenting manifestations of APS are deep vein thrombosis (31.7% of patients), thrombocytopenia (21.9%), livedo reticularis (20.4%), and stroke (13.1%). Less frequent manifestations include superficial thrombophlebitis (9.1%), pulmonary embolism (9%), transient ischemic attacks (7%), and hemolytic anemia (6.6%). Fetal loss is the presenting manifestation in 14% of female patients. Although the clinical profiles of primary APS and SLE associated APS are similar, some features such as hemolytic anemia,neutropenia, lymphopenia and heart valve disease are significantly more frequent in the latter group of patients.[42]

CUTANEOUS MANIFESTATIONS OF ANTIPHOSPOLIPID SYNDROME

Dermatological manifestations may be the presenting feature in primary APS and it can be the first clue in the diagnosis of this disease.[43] So it is important to investigate patients who present with cutaneous manifestation related to venous or arterial thrombosis or microthrombosis.

The cutaneous manifestations of APS are listed in Table 4.

Various studies have shown the frequency of dermatological manifestations with APS.

Weinstein *et al.*[43] report that livedo reticularis or racemosa is commonly seen in APS, but is one of the least specific findings and APS should be considered in patients who have idiopathic livedo reticularis with cerebrovascular accidents (Sneddon's syndrome), atrophie blanche, livedoid vasculitis, malignant atrophic papulosis, or anetoderma. Retiform (branching, stellate) purpura or necrosis is the most characteristic cutaneous lesion of many different cutaneous microvascular occlusion syndromes, including APS.

Diogenes *et al.*[3] report 40 cases in which the most common dermatological manifestation was dermographism followed by acrocyanosis, urticaria, diffuse alopecia, livedo reticularis, ulcers and necrosis, nodules, Raynaud's phenomenon, purpura, pterygium unguium and subungual hemorrhage.

According to a study by Diallo *et al.*[44] the most common presentation is necrosis of the extremities followed

Table 4: Cutaneous manifestations of APS

Cutaneous manifestations	Reference number
Livedo reticularis	43
Atrophie blanche	43
Livedoid vasculitis	43
Malignant atrophic papulosis	43
Anetoderma	43
Cutaneous ulcers	44
Acrocyanosis	44
Subungual splinter hemorrhage	44
Digital gangrene	45
Superficial venous thrombosis	45
Dermographism	3
Diffuse alopecia	3
Raynaud's phenomenon	3
Bullous systemic lupus erythematosus	46
Rheumatoid nodules	47
Granuloma pyogenicum	48
Interstitial granulomatous dermatitis	49
Autoimmune blistering disease	50

by purpuric lesions, cutaneous ulcers, acrocyanosis, livedo and subungual splinter hemorrhage.

Toubi *et al*.[51] report that livedo reticularis is a marker for predicting multi-system thrombosis in antiphospholipid syndrome.

MANAGEMENT OF ANTIPHOSPOLIPID SYNDROME

The management of antiphospolipid syndrome involves primary thromboprophylaxis and secondary management of thromboembolic events.

PRIMARY THROMBOPROPHYLAXIS

Primary thromboprophylaxis with low dose aspirin is instituted in patients with aPL and no thrombotic events. Wahl *et al*.[52] have shown that low dose aspirin can be used in the primary thromboprophylaxis but a recent study by Erkan *et al*.[53] and the Physician health study[54] shows that aspirin is not useful in preventing thrombus formation. The controversy over thromboprophylaxis requirement in patients who are asymptomatic with aPL remains unsolved. Rand *et al*.[55] proved that hydroxychloroquine reduces the formation of aPL--β2GPI complexes to phospholipid bilayers and can be used in thromboprophylaxis in APS.

Cessation of oral contraceptive,treatment of hypertension and hyperlipidemia and avoidance of smoking are additional measures to reduce the thromboembolic events.

SECONDARY THROMBOPROPHYLAXIS

Secondary thromboprophylaxis refers to the 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 of APS.[56]

The current recommendation for secondary thromboprophylaxis is life long warfarin.[57] When using oral anticoagulation with warfarin, most clinicians favor keeping the international normalized ratio (INR) between 2.0 and 3.0 to avoid hemorrhagic complications. Every 1-point rise in INR increases the risk for major bleeding by 42%[58] and high-intensity anticoagulation carries an increased risk of bleeding.[59] A recent prospective randomized controlled trial on the efficacy and safety of high-intensity warfarin treatment (target INR, 3.0-4.0) versus standard-intensity treatment (target INR, 2.0-3.0) in 114 patients with aPLs and thrombosis showed that there was no difference in the rates of recurrent thrombosis and bleeding between the two groups.[60]

Low-molecular-weight heparin is used instead of warfarin for treatment during pregnancy.[61] Noble *et al*.[62] have compared low molecular weight heparin and unfractionated heparin along with low dose aspirin in the treatment of APS-associated recurrent pregnancy loss and concluded that low-molecular-weight heparin is as safe as unfractionated heparin for the prevention of recurrent pregnancy loss.

Antiplatelet agents such as dipyridamole, aspirin with dipyridamole, ticlopidine or clopidogrel bisulfate have been used for secondary prevention after non-cardioembolic strokes or TIA.[63] Intravenous immunoglobulin (IVIg) has also been used in the treatment of thrombotic events in APS.[64]

Recently, rituximab, a monoclonal antibody that selectively depletes $CD20^{+}$ B cells, has been successfully employed to treat thrombocytopenia in a small number of patients with resistant APS.[65]

CONCLUSION

Antiphospholipid antibodies have long been recognized. However, it was only recently discovered that the antigenic targets of these antibodies were, in fact, plasma proteins or complexes of these proteins with phospholipids. This led to expansion of the scope of research on aPL. It has now been established that aPLs, through multiple mechanisms, act on the coagulation system, the fibrinolytic system, platelets and endothelial cells. Laboratory detection of aPL has also changed radically with the recognition of their antigenic targets. APS can affect any organ or system and although dermatological manifestations are not included in the classification criteria, they may be the presenting feature of this syndrome.

Prognosis primarily depends on the severity of the clinical manifestations and, therefore, knowledge of the presentation and manifestations of this disease is critical in early detection and prompt treatment to

prevent life-threatening consequences of this disease process.

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Multiple Choice Questions

1. Dilute russel viper venom test is used to diagnose
   a. Anticardiolipin antibodies
   b. Antibodies against Prothrombin
   c. Lupus anticoagulant
   d. anti-β_2-glycoprotein I antibodies

2. APS is characterized by all except
   a. Thrombosis in arteries
   b. Thrombosis in vein
   c. Microthrombi
   d. Superficial vein thrombosis

3. Antiphospholipid antibodies may be transient in all except
   a. Patients with SLE
   b. Normal individuals
   c. Pregnancy
   d. Elderly population

4. Immunoassays detect all except
   a. Lupus anticoagulant
   b. anti-β_2-glycoprotein I antibodies
   c. Antibodies against phospholipids other than cardiolipin
   d. Antibodies against phospholipids-binding plasma proteins

5. The most common cutaneous manifestation with APS
   a. Livedoid vasculitis
   b. Cutaneous ulcers
   c. Livedo reticularis
   d. Acrocyanosis

6. The current recommendation for secondary thromboprophylaxis
   a. Heparin
   b. Warfarin
   c. Aspirin
   d. Hydroxylchloroquine

7. When using oral anticoagulation with warfarin, international normalised ratio (INR) should be maintained between
   a. 1-2
   b. 2-3
   c. 3-4
   d. 4-5

8. By which of the following mechanisms do antiphospholipid antibodies cause hypercoagulable state ?
   a. Interference with coagulation cascade
   b. Activation of endothelial cells
   c. Oxidant-mediated injury of the vascular endothelium
   d. All the above.

9. What are the clotting factors in the extrinsic pathway that require phospholipids for activation?
   a. IX
   b. X
   c. XII
   d. IX and X

10. Which of the following are the targets of antiphospholipid antibodies?
    a. anionic phospholipids
    b. β_2-glycoprotein
    c. Protein C, and S
    d. All the above

Answers

1. c, 2. d, 3. a, 4. a, 5. c, 6. b, 7. b, 8. d, 9. d, 10. d