# 22 Antiphospholipid Syndrome: Differential Diagnosis

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## Introduction

Reaching the correct diagnosis is the aim of every physician. This chapter is designed to ensure that the correct diagnosis is achieved in patients whose differential diagnosis includes antiphospholipid syndrome (APS). In the past, APS was often not considered in the differential diagnosis of a thrombotic state, although this has occurred less frequently as the condition is becoming better known and understood. Lack of understanding of the assays can result in interpretation difficulties, particularly if investigators do not appreciate that both lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) are different facets of the same problem, and that both must be performed to exclude the diagnosis.

If physicians read this particular book, then they will consider APS in the differential diagnosis of thrombotic disease, and should be highly skilled at interpreting the antiphospholipid (aPL) assays. However, there is a possibility of "overdiagnosis," which is as important to avoid as non-recognition, for once a diagnosis of APS has been made, the management of thrombosis in APS is not without recognized morbidity and mortality due to bleeding. Thus, in patients with aPL, it is important to establish from the history, examination, and investigations that the associated clinical features are consistent with APS, that the aPL assays are reproducible, and that there is no other explanation for the thrombotic events.

In view of the diverse presentation of APS, we have planned this chapter taking into account the new international consensus statement on preliminary criteria for the classification of the APS [1].

## Clinical Criteria

### Vascular Thrombosis

"One or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For

histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall."

## The Differential Diagnosis of Venous Thrombosis

Any part of the venous circulation may undergo occlusion in APS. Deep and superficial veins of the lower limbs are most frequently involved, followed by pulmonary embolism and arm vessels. In these instances, and in subjects who are relatively young (< 45 years), the differential diagnosis rests on laboratory tests aiming at the identification of congenital or other acquired thrombophilic states. The current venous thrombophilia screen (1999) is shown in Table 22.1. aPL seems to be a common etiological factor in venous thrombosis in unusual sites such as the abdominal circulation. APS has been described as the second most common cause of Budd-Chiari syndrome [2], after myeloproliferative disorders [3], and thrombosis in other abdominal veins are reported in APS. APS should be included in the differential diagnosis of cerebral vein thrombosis, because the presence of aPL in this population ranges from 8% to 55%, and affected patients tend to have younger age at onset and more extensive involvement than patients with conventional thrombophilic states [4, 5]. Consideration should be given to the prothrombin 20210 mutation, present in 2% of Caucasians, that also appears to predispose to thrombosis in the coronary and cerebral venous vessels. The differential effects of hypercoagulable states in different vascular beds is excellently reviewed by Rosenberg and Aird [6]. In the ophthalmology setting, aPL have been detected from 5% to 47% of subjects presenting with retinal vein occlusion, alongside other thrombophilic factors and vasculitis [7–9]. aPL should be included in the differential diagnosis of thrombotic events causing endocrine abnormalities, such as Addison's disease [10–12] and Sheehan's syndrome (hypopituitarism) [13]. Although the differential diagnosis of venous occlusions often relies on detecting a thrombophilic state, some clinical features may point towards systemic disorders with a higher-than-average risk of venous thrombosis. For example, a history of oral and genital ulceration in a young person with venous thrombosis may suggest Behcet's disease, and the presence of peripheral blood eosinophilia could suggest

**Table 22.1.** Differential diagnosis of venous thromboembolism in antiphospholipid syndrome.

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| Activated protein C resistance/factor V Leiden (heterozygote and homozygous) |
| Heterozygous deficiencies of<br>Antithrombin<br>Protein C<br>Protein S<br>Prothrombin 20210 heterozygous or homozygous states |
| Increased levels of factor VIII |
| Myeloproliferative disorders |
| Dysfibrinogenemia |
| *Very rare*<br>Paroxysmal nocturnal hemoglobinuria |
| *Possible risk factor*<br>Hyperhomocysteinemia |