45 Management of Thrombocytopenia in Hughes Syndrome

Monica Galli and Tiziano Barbui

Introduction

The combination of lupus anticoagulants (LA) and anticardiolipin antibodies (aCL), which are the best known antiphospholipid antibodies (aPL), with arterial and venous thrombosis and recurrent miscarriages defines Hughes syndrome. Two forms of Hughes syndrome have been described: the "primary" syndrome [1], that occurs in the absence of any underlying disease, and the "secondary" syndrome [2], that develops in association with another pathological condition, mainly systemic lupus erythematosus (SLE). In 1999, a panel of experts defined the preliminary laboratory and clinical criteria for Hughes syndrome [3].

Thrombosis is the most frequent clinical event of Hughes syndrome, as it occurs in approximately 30% of patients [4], with an overall annual rate of 2.5% [5]. Venous thrombosis accounts for about 60% of all thromboembolic events, and is represented mainly by deep vein thrombosis of the legs and pulmonary embolism [6]. On the other hand, complete cerebral ischemic strokes and transient ischemic attacks are the most common arterial thrombosis [6]. Thrombosis may be recurrent and is often spontaneous. Obstetric complications are reported in about 15% to 20% of women with Hughes syndrome [7], and are considered secondary to thrombosis of the placental vessels [8].

A variable degree of thrombocytopenia is observed in as many as 20% to 40% of patients with aPL [9]. As uncertainty exists regarding its pathogenesis, therapy, and influence on the policy of treatment of thrombosis, the panel of experts decided not to include thrombocytopenia among the criteria for the diagnosis of Hughes syndrome.

Pathophysiology of Thrombocytopenia

Thrombocytopenia of Hughes syndrome is classified among the immune thrombocytopenias. Idiopathic thrombocytopenic purpura – the most common and better known of this group of conditions – has been pathogenetically linked to specific autoantibodies directed against glycoproteins IIb/IIIa and Ib/IX (less frequently, also glycoproteins Ia/IIa and V) [10]. Upon binding to platelet membrane, these

Table 45.1. Antigenic targets of antiphospholipid antibodies.

β_2-glycoprotein I
(Human) prothrombin
(Activated) protein C
Protein S
Tissue-type plasminogen activator
Annexin V
Thrombomodulin
Oxidized low-density lipoproteins
Factor XII
High- and low-molecular weight kininogens
Factor VII/VIIa
Complement components H and C4b

antibodies increase the peripheral destruction of opsonized platelets [11, 12]. Typically, the half-life of platelets becomes very short, and their scavenging from circulation takes place mainly in the spleen and the liver.

In the mid 1980s, aPL had been suggested to cause thrombocytopenia, based on the high prevalence of aCL in patients with idiopatic thrombocytopenic purpura [13], and on the interaction between platelet membrane phospholipids and these antibodies (see below). Even though this possibility cannot be excluded, the direct role of aPL in the pathogenesis of thrombocytopenia has been questioned. In fact, antibodies directed against glycoproteins IIb/IIIa and Ib/IX are found in about 40% of aPL-positive patients [14], a figure similar to that already known for idiopathic thrombocytopenic purpura [15]. Moreover, antibodies directed against a 50–70 kDa internal platelet protein have been specifically found in patients with aPL and thrombocytopenia but not in patients with idiopathic thrombocytopenic purpura [16]. Antibodies directed towards platelet glycoproteins Ia/IIa and IV and towards CD9 have also been detected in the serum of patients with primary Hughes syndrome [17]. Finally, it has been observed that immunosuppressive treatment of idiopathic thrombocytopenic purpura increased platelet number and reduced the titers of platelet-associated IgG but not those of aPL [18]. This data would indicate that aPL and antiplatelet antibodies comprise different specificities and suggest that platelet-specific antibodies, rather than aPL, play a role in the pathogenesis of thrombocytopenia of Hughes syndrome.

Interactions Between aPL Antibodies and Platelets: Parallelism with Heparin-induced Thrombocytopenia

aPL interact with negatively charged phospholipids by means of specific proteins (listed in Table 45.1). β_2-glycoprotein I and prothrombin are by far the 2 best known and characterized antigenic targets of aPL [19–22].

Anionic phospholipids are essential constituents of cell membranes. In platelets, they are located in the inner leaflet of the plasma membrane [reviewed in 23]; thus, they are not available for interaction with aPL. However, under physiologic conditions, this asymmetric distribution can be lost, resulting in exposure of anionic phospholipids on the outer leaflet of plasma membrane [23]. For platelets, this phenomenon occurs upon activation by different agonists and is accompanied by shed-