4 Hemocytopenias in Antiphospholipid Syndrome

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Introduction

Although not included in the recently proposed preliminary criteria for the classification of the human antiphospholipid (Hughes) syndrome (APS) [1], thrombocytopenia is one of the most common laboratory abnormalities found in patients with APS [2, 3], and it is present in some animal models as well [4, 5]. Hemolytic anemia can also be found in APS although less frequently than thrombocytopenia [2, 3]. These hemocytopenias are mainly due to autoimmune mechanisms as supported by the presence of bone marrow megakaryocytes and platelet-associated immunoglobulins for thrombocytopenia and by increased reticulocytes and positive direct Coombs' test for hemolytic anemia. However, antiphospholipid antibodies (aPL) were also reported in association with thrombotic thrombocytopenia and microangiopathic hemolytic anemia.

The present chapter deals with the clinical features of aPL-associated cytopenia, either autoimmune or thrombotic/microangiopathic.

Autoimmune Thrombocytopenia

Prevalence in Primary and Secondary APS

A correlation between thrombocytopenia and aPL is well documented in spite of differences related to the criteria of patient selection and the methods employed to detect aPL. Thrombocytopenia was found in 26% of cases in a series of 319 patients with positive test for either lupus anticoagulant (LA) or anticardiolipin antibodies (aCL) collected from the Italian Registry of aPL [6]. This series included 112 patients with systemic lupus erythematosus (SLE) and 207 with primary APS (PAPS) or without any clinical syndrome. A multicenter study by Vianna et al [7] showed thrombocytopenia in 40% of patients with either PAPS or APS secondary to SLE. Recently, in a large cohort of patients with APS (either PAPS or APS secondary to SLE) from 13 European countries, thrombocytopenia was found in about 30% of cases, and was one of the most common presenting manifestation [2].

In SLE, thrombocytopenia is significantly more frequent in patients with aPL than in patients without [8, 9]; the patients with both LA and high aCL show the highest frequency of thrombocytopenia [10]. Among patients with APS, thrombocytopenia is more frequently observed in patients with SLE than in patients with PAPS [2]. In a recently published paper, McClain et al showed that the presence of aPL may precede the diagnosis of SLE and that, in these patients, thrombocytopenia was common and occurred earlier than in aPL-negative patients [11].

In pediatric APS the presence of thrombocytopenia was either confirmed [12, 13] or denied [14]. Recently, thrombocytopenia was found in 17 out of 58 (29%) of pediatric patients with APS (5 with PAPS and 12 with SLE or SLE-like disorders) [15]. In this cohort, thrombocytopenia was the most frequent APS-related manifestation observed. In SLE pediatric patients, thrombocytopenia has been reported much more frequently in patients with clinical features of APS than in other SLE patients, with or without the presence of aPL [16].

A close correlation with thrombocytopenia was reported for other markers of APS such as antimithocondrial antibodies type-M5 [17] and antibodies reacting to thromboplastin in a solid phase assay [18]. Anti-prothrombin antibodies seem to be associated with thrombocytopenia in patients with PAPS but not in patients with APS secondary to SLE [19].

On the contrary, the antibodies to oxidated low-density lipoproteins do not correlate with thrombocytopenia [20]. A strong relationship between APS features, including thrombocytopenia, and antibodies to β_2-glycoprotein I (β_2-GPI) has been reported by different groups [21, 22]. Anti–β2-GPI seems to show higher specificity but lower sensitivity for thrombocytopenia with respect to aCL or LA [23].

Many papers have addressed the relationship between aCL specific isotypes and thrombocytopenia. Most of these studies showed a stronger correlation with IgG [24, 25]; the usefulness of testing for IgA aCL and IgA anti–β2-GPI is still a matter of debate [26, 27].

Clinical Features

aPL–related thrombocytopenia is a chronic, usually mild form and is seldom associated with hemorrhagic complications. Values lower than 50×10^9 platelets/L are uncommon, although platelet count can fluctuate with time. Among the patients enrolled in the Italian Registry of aPL [6], 32 (11%) had severe thrombocytopenia and only two experienced bleeding. In a cohort of 305 patients with SLE, severe thrombocytopenia was found in 20 patients and was strongly associated with the presence of aCL [28].

It should be kept in mind that bleeding may be related to several causes other than thrombocytopenia: (a) high-intensity oral anticoagulation for thromboembolic disease; (b) hypoprothrombinemia, which has been reported in patients with LA and hemorrhagic complications; (c) acquired defects of platelet function which may be associated with aPL. Severe thrombocytopenia is likely to act as an additional risk factor for bleeding complications in these patients and it might explain a higher than expected incidence of life-threatening bleeding events in APS patients on high-intensity warfarin therapy [29].

Arterial and/or deep venous thrombosis in APS may occur despite very low platelet count; however, the frequency of aPL-associated thrombotic events may be lower when platelet count is less than 50×10^9/L [6].