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Original article

Thrombocytopenia as a thrombotic risk factor in patients with antiphospholipid antibodies without disease criteria☆

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ABSTRACT

Introduction: The antiphospholipid syndrome (APS) is an acquired immune disorder defined by the presence of thrombosis (arterial and/or venous) and/or pregnancy morbidity along with the presence of positive antiphospholipid antibodies (aPL). There is a clear relationship between aPL and some events not included in the clinical criteria, including haematologic.
Objectives: (a) to study the probability of developing clinical APS in patients with positive aPL and thrombopenia; (b) to identify potential risk factors for thrombosis, and (c) to study the association between thrombocytopenia and aPL.
Methods: A retrospective study of 138 patients with positive aPL without fulfilling clinical criteria for APS. Thrombocytopenia was defined as a platelet count $\leq$100,000/μl. Patients with other causes of thrombocytopenia were excluded.
Results: Seventeen of the 138 (12%) patients in the study had thrombocytopenia. The mean platelet count was 60,000/μl. The risk of developing thrombocytopenia was higher in smokers (OR 2.8; $p = 0.044$), in those with lupus anticoagulant (OR 13.5; $p < 0.001$) and those with higher burden of aPL (OR 50.8; $p < 0.001$). After a mean follow-up of 146 ± 60.3 months, 5 patients with thrombocytopenia (29.4%) developed thrombosis.
Conclusions: In our series, the incidence of thrombocytopenia is 12%. aPL-positive patients who develop thrombocytopenia have a potential risk of developing thrombosis. Tobacco could be a risk factor for thrombocytopenia. Autoantibodies load is a risk factor for the development of thrombocytopenia.

Trombocitopenia como factor de riesgo trombótico en pacientes con anticuerpos antifosfolipídicos sin criterios de enfermedad

Palabras clave:
Síndrome antifosfolípido
Trombocitopenia
Anticuerpos antifosfolipídicos

RESUMEN

Introducción: El síndrome antifosfolípido (SAF) es un trastorno inmunitario adquirido, definido por la presencia de trombosis (arterial y/o venosa) y/o morbilidad del embarazo junto con la presencia de anticuerpos antifosfolipídicos (aFL) positivos. Existe una relación clara entre los aFL y algunas manifestaciones no incluidas en los criterios clínicos, entre ellas, las hematológicas.

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Objetivos: a) estudiar la probabilidad de desarrollar SAF clínico en pacientes con aFL positivos y trombocitopenia; b) identificar posibles factores de riesgo para trombosis, y c) estudiar la asociación entre trombocitopenia y aFL.
Métodos: Estudio retrospectivo de 138 pacientes con aFL positivos sin cumplir criterios clínicos de SAF. Se definió trombocitopenia como una cifra de plaquetas ≤100.000/μl. Se excluyeron los pacientes con otras causas de trombocitopenia.
Resultados: Diecisiete de los 138 (12%) pacientes incluidos en el estudio presentaban trombocitopenia. La cifra media de plaquetas fue de 60.000/μl. El riesgo para desarrollar trombocitopenia fue mayor en los pacientes fumadores (OR 2,8; p = 0,044), en aquellos con anticoagulante lúpico (OR 13,5; p < 0,001) y en los que tenían una mayor carga de aFL (OR 50,8; p < 0,001). Tras un seguimiento medio de 146 ± 60,3 meses, 5 pacientes con trombocitopenia (29,4%) desarrollaron trombosis.
Conclusiones: En nuestra serie, la incidencia de trombocitopenia es del 12%. Los pacientes con aFL positivos que desarrollan trombocitopenia tienen un riesgo potencial de desarrollar trombosis. El tabaco podría ser un factor de riesgo para trombocitopenia. La carga de autoanticuerpos es un factor de riesgo para el desarrollo de trombocitopenia.

Introduction

Antiphospholipid syndrome (APS) is an acquired immune disorder, defined by the occurrence of arterial or venous thrombosis or pregnancy morbidity, plus the occurrence of positive antiphospholipid antibodies (aPL), such as anticardiolipin (aCL), anti-beta2 glycoprotein 1 (AB2GPI) or lupus anticoagulant (LA) antibodies.

The diagnosis of APS requires both clinical evidence (thrombosis or obstetric disease) and analytical evidence (verified and repeated presence of aPL). This has been stated in the Sapporo international consensus,[1] subsequently revised in Sydney.[2]

On the other hand, aPL and other manifestations not included in the clinical criteria are correlated,[3] such as heart valve lesions, nephropathy, livedo reticularis and hematological manifestations. Of the hematological manifestations, thrombocytopenia has been described in 20–50% of patients with APS.[4,5] However, it is not part of the definitive criteria,[2] even though it was suggested in the preliminary criteria.[6] Several studies have been published on the prevalence of thrombocytopenia in APS.[7–9] This has been reported by Cervera et al. in a detailed review of the medical literature concluding thrombocytopenia is associated in 20–53% of 2900 patients from the total of the analyzed studies with primary or secondary APS. Some authors show higher incidences in those with associated systemic lupus erythematosus (SLE),[3] while others do not report these differences.[9]

Severe thrombocytopenia in APS is uncommon, and bleeding is much more rare than thrombosis, but it might be a problem when having to a patient. Significant bleeding usually occurs with platelet counts below 20,000, and is rare in cases of APS, where thrombocytopenia is generally over 50,000 platelets and does not require therapeutic intervention in most cases.[9] Idiopathic thrombocytopenic purpura (ITP) is an acquired autoimmune disorder characterized by the presence of autoantibodies against platelet membrane glycoproteins, in the absence of other causes of thrombocytopenia, which leads to an increased platelet destruction. aPLs are frequently found in patients with ITP, with a prevalence ranging from 25% to 75% in the literature.[10–14] Bidot et al.[13] found an 86% exacerbation rate compared to 42% remissions.

The pathogenesis of aPL-associated thrombocytopenia is partly uncertain and may be due to combined mechanisms of increased destruction and/or decreased production.

On the one hand, aPLs are bound to activated platelets via platelet membrane B2GPI[16] stimulating activation and aggregation. On the other hand, platelet destruction can be produced by direct antibodies against the membrane glycoproteins, which increase their expression in the presence of aPLs. Thrombocytopenia in APS has also been associated with the presence of these platelet antiglycoprotein antibodies: GPIIb/IIIa, GPIb/IX, GPIa/IIa, GPIV, the main one being GPIIb/IIa.[17] It appears that severe thrombocytopenia in APS is better related to these antiplatelet antibodies than to aPL.[18] Currently the diagnosis of ITP remains a diagnosis of exclusion.[19]

This study is aimed at studying the probability of developing clinical APS in patients with positive aPL and thrombocytopenia, to analyze thrombocytopenia as a potential risk factor for thrombosis or obstetric disease, and to study the association of thrombocytopenia with one of the types of aPL and with the autoantibody load.[20]

Material and methods

Patient selection

Retrospective data were collected from 138 patients with positive serology for APS on at least 2 occasions and 12 over weeks apart at moderate or high titers, not complying with clinical criteria for APS. Patients were recruited from the database of the Immunology Service of the University Hospital Marqués de Valdecilla. We reviewed 1200 positive aPL serologies from 1999 to 2004. Exclusion criteria included those patients with clinical symptoms of APS included in the clinical criteria, absence of positive confirmation for serology, as well as low titers for such positivity. We obtained a total of 138 patients with analytical criteria, but not clinical criteria. LA data were available in 89 of these patients. Of these 138 patients, 17 associated thrombocytopenia ≤100,000 as hematologic symptomatology. Patients with other causes of thrombocytopenia, such as bone marrow disease, hepatopathy, disseminated intravascular coagulation or thrombotic thrombocytopenic purpura were excluded. The study complies with the principles of the Declaration of Helsinki and was approved by the Ethics Committee on Clinical Research of Cantabria.

Clinical data

The clinical data of the patients were obtained through a careful review of the medical history retrospectively. Demographic data (age and sex), cardiovascular risk factors (hypertension, diabetes, cholesterol, smoking), associated diseases, thrombophilia, presence of aPL (aCL IgG/M, AB2GPI IgG/M, lupus anticoagulant [LA]), development of thrombosis, association of thrombocytopenia or obstetric disease, as well as the treatment received.

Thrombocytopenia was defined as a number below or equal to 100,000 platelets.[15]