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Risk factors and clinical profile of thrombotic thrombocytopenic purpura in systemic lupus erythematosus patients. Is this a distinctive clinical entity in the thrombotic microangiopathy spectrum?: A case control study

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ABSTRACT

Introduction: The association of thrombotic thrombocytopenic purpura (TTP) with systemic lupus erythematosus (SLE) is rare. It is associated with high morbidity and mortality. Information about risk factors and clinical outcomes is scant.

Material and Methods: A retrospective case-control study was performed in a referral center in Mexico City between 1994 and 2013. Patients were diagnosed with TTP if they fulfilled the following criteria: microangiopathic haemolytic anaemia, thrombocytopenia, high LDH levels, normal fibrinogen and negative Coombs' test. Patients with SLE were diagnosed with ≥4 ACR criteria. We included three study groups: group A included patients with SLE-associated TTP (TTP/SLE; cases n = 22, TTP events n = 24); patients with non-autoimmune TTP (NA-TTP; cases n = 19, TTP events n = 22) were included in group B and patients with SLE without TTP (n = 48) in group C.

Results: After multivariate analysis, lymphopenia <1000/mm3 [OR 19.84, p = 0.037], high SLEDAI score three months prior to hospitalisation [OR 1.54, p = 0.028], Hg <7 g/dL [OR 6.81, p = 0.026], low levels of indirect bilirubin [OR 0.51, p = 0.007], and less severe thrombocytopenia [OR 0.98, p = 0.009] were associated with TTP in SLE patients. Patients with TTP/SLE received increased cumulative steroid dose vs. NA-TTP (p = 0.006) and a higher number of immunosuppressive drugs (p = 0.015). Patients with TTP/SLE had higher survival than NA-TTP (p = 0.033); however, patients hospitalised for TTP/SLE had a higher risk of death than lupus patients hospitalised for other causes

Conclusions: Lymphopenia is an independent risk factor for TTP/SLE. It is likely that patients with TTP/SLE present with less evident clinical features, so the level of suspicion must be higher to avoid delay in treatment.

Introduction

Moschowitz [1] first described what is known today as thrombotic thrombocytopenic purpura (TTP)- it is a rare disease [2] (about 3.7 cases per million people per year) characterised by microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, fever, renal dysfunction and neurological symptoms. TTP can be subdivided in idiopathic, congenital or associated with other conditions (human immunodeficiency virus, pregnancy, drugs, transplantation or malignancy) [3]. There are many differential diagnoses of TTP, including disseminated intravascular coagulation, systemic infections, drugs, catastrophic antiphospholipid syndrome, among others [4]. A close relationship has been found between TTP and some systemic autoimmune diseases [5]. Particularly, the association between TTP and systemic lupus erythematosus (SLE) is often difficult to diagnose, since

Abbreviations: TTP, Thrombotic Thrombocytopenic Purpura; HIV, Human Immunodeficiency Virus; SLE, Systemic Lupus Erythematosus; MAHA, microangiopathic haemolytic anaemia; TMA, thrombotic microangiopathy; PE, plasma exchange; APS, antiphospholipid syndrome; LDH, lactate dehydrogenase; Ap13, ADAMTS13 plasmatic activity; NA-TTP, non-autoimmune TTP; vWf, von Willebrand factor; IFI 16, Interferon Gamma-Inducible protein 16; OR, Odds Ratio.

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both disorders share similar clinical features and laboratory parameters [6,7]. This can delay the initiation of optimal treatment and directly influence prognosis. While the association between these two diseases seems to be very rare (2%) [8], two classic postmortem studies showed the epidemiological association between SLE and TTP. First, Levine et al. [9] found that 34 of 151 (23%) deaths attributed to TTP had histopathological data compatible with SLE. Subsequently, Devinsky et al. [10] showed that 28% of autopsies from patients with SLE had postmortem features that suggested TTP. In only one of these cases the suspicion of TTP associated with SLE was prior to the patient's death; the rest of the patients were misdiagnosed. Although they all were treated with high-dose glucocorticoids, none was treated with plasma exchange (PE). This opens the possibility that SLE-associated TTP remains underdiagnosed, leading to delayed and usually suboptimal treatment. Early initiation of PE therapy in TTP has shown to decrease mortality to <20% [11]. Therefore, some authors have recommended starting treatment with PE if there is suspicion of TTP based on the single presence of MAHA and thrombocytopenia [12–14], without other obvious causes.

In the main series of TTP in SLE patients [8,15], the presence of nephritis and SLEDAI score >10 (see Appendix A) [16] points are the only recognized independent risk factors for this association. Besides, infections have proven to be a trigger for TTP in SLE patients and also the most frequent cause of death [8], along with neurological involvement [17]. In 2005 Dold et al. [18] aimed to characterise distinctive features between SLE haematological activity and MAHA. They concluded that in the presence of MAHA and moderate thrombocytopenia, patients could be treated solely with high-dose glucocorticoids alone. It is worth mentioning that patients with more severe clinical manifestations were treated with PE. Therefore, it is crucial to make a prompt diagnosis based on high clinical suspicion in order to start an optimal treatment without delay.

While up to 40% of patients with SLE have antiphospholipid antibodies [19], the main reports of TTP and SLE exclude patients with positive serology [15], and other studies have not found a significant association with the antiphospholipid antibody profile [8,20]. On the other hand, Musio et al. [21] considered antiphospholipid syndrome (APS) not only as a differential diagnosis necessary to be taken into account, but also that these antibodies could play a direct role in thrombogenesis and endothelial damage. In their review study of 40 patients, 50% of cases with TTP/SLE showed positive serology for APS, suggesting a contribution to the development of thrombotic microangiopathy. However, this issue remains controversial.

Even though the association with TTP has an impact on morbidity and mortality in SLE patients, current evidence regarding potential risk factors and the clinical outcomes of TTP in SLE continues to be scant. The aim of this study was to analyse potential risk factors, as well as clinical characteristics and outcomes of TTP in patients with SLE.

Material and Methods

We performed a retrospective case-control study that included 92 patients. We defined three study groups: group A (cases) and groups B and C (controls). Group A included patients with SLE-associated TTP (TTP/SLE; cases n = 22, TTP events n = 24). Patients with non-autoimmune TTP (NA-TTP; cases n = 19, TTP events n = 22) were included in group B and patients with SLE without TTP (n = 48) in group C.

We reviewed the clinical records of patients admitted to the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care center in Mexico City. Records were reviewed over a 19-year period (from January 1994 to June 2013). Cases (group A) included patients that were diagnosed with SLE if they fulfilled at least four American College of Rheumatology (ACR) classification criteria (see Appendix B) [22]. In these patients, TTP was diagnosed if they showed all of the following features: microangiopathic haemolytic anaemia (one or more schistocytes per field), thrombocytopenia <100,000 cells/ μl, elevated LDH (50% or more from upper limit value) [12,13], normal fibrinogen and negative Coombs' test. The TTP diagnosis was corroborated by the opinion of an expert haematologist in the field (R.D.G.). As controls (group B), we included patients who fulfilled the aforementioned TTP criteria, without evidence of any systemic autoimmune disease prior or during the follow-up. TTP events associated with pregnancy, cancer, drugs and human immunodeficiency virus (HIV), as well as idiopathic cases, were included. Finally, group C included patients with diagnosis of SLE without TTP that were hospitalised during the same period as cases (+/- 4 weeks). They were adjusted by gender and were chosen randomly. The investigators were blinded to the hospitalisation cause, in order to avoid bias. Patients with a diagnosis of other systemic autoimmune disease (except APS) or any other cause of persistent thrombocytopenia (cirrhosis, other causes of hypersplenism, immune primary thrombocytopenia, sepsis, vitamin deficiencies, bone marrow failure, infections or drugs) were excluded from the study. The remission criteria of TTP were defined as two consecutive determinations of platelets ≥150,000 cells/ μl with normal levels of lactate dehydrogenase (LDH) and without schistocytes in peripheral blood smear [3]. When available, ADAMTS13 plasmatic activity (Ap13) was determined in patients with TTP (ELISA, Quest Diagnostics Nichols Institute San Juan Capistrano, CA), as well as antibodies against ADAMTS13 (ELISA IgG type, BloodCenter of Wisconsin) in TTP/SLE patients.

The study was approved by the institutional ethics committee. Variables are described in terms of mean, median and standard deviation (SD), or proportions, as convenient. For the comparison between groups, χ^2 test for categorical variables and Student's t test for continuous variables were used. Also, association was addressed by odds ratio (OR) with 95% confidence interval (CI). The variables that were statistically significant in the univariate analysis or those that might have clinical relevance were included in the multivariate analysis that was performed by means of binary logistic regression. Analysis of survival was made by Kaplan-Meier method and log rank test. P values <0.05 were considered as statistically significant. Data were analysed with the support of the statistical software SPSS version 21.

Results

Demographic, clinical and laboratory features

Most cases of TTP were women (100% cases and 78% in control group). Patients with TTP/SLE were significantly younger than controls (29.7 ± 2.1 vs. 40.6 ± 3.2 years; p = 0.006). The frequency of each subset of NA-TTP was: 15 idiopathic, 5 associated with pregnancy (one with HELLP syndrome), one with HIV and one with cancer. There were no significant differences among clinical manifestations of TTP/SLE and those of NA-TTP. The clinical and laboratory parameters are shown in Table 1. We observed a higher amount of schistocytes per field on peripheral blood smear in TTP/SLE patients compared with NA-TTP (p = 0.046) at diagnosis. However, the main laboratory parameters used to assess haemolysis (reticulocyte index, LDH levels and bilirubin) were significantly lower in the TTP/SLE group when compared to the NA-TTP group. Furthermore, all SLE patients with TTP had positive antinuclear antibodies (ANAs), the most frequent patterns were: homogenous (59.09%) and fine speckled (31.81%). Other autoantibodies that have been related to SLE diagnosis or activity such as anti-Smith (anti-Sm) were positive in 40.90% of SLE patients with TTP and 33.33% of SLE patients without TTP. Anti-Ro antibodies were the other autoantibodies more frequently encountered in SLE-TTP (50%). Furthermore, we found increased levels of anti-Ro in SLE patients with TTP in comparison to SLE patients without TTP (608.54 ± 356.83 vs 8.17 ± 3.24 U/mL, p = 0.047). Meanwhile, no differences were found in anti-Sm titers between groups. Therefore, TTP-SLE patients were characterised by the positivity of ANAs, as well as the presence of high titers of anti-Ro.