Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Review Article - Meta-analysis

Microangiopathic Hemolytic Anemia in Systemic Lupus Erythematosus: Narrative Review☆

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ARTICLE INFO

Article history:
Received 12 April 2015
Accepted 18 May 2015
Available online 3 July 2015

Keywords:
Systemic lupus erythematosus
Lupus
Thrombotic thrombocytopenic purpura
Microangiopathic haemolytic anaemia

ABSTRACT

Introduction: The clinical spectrum of microangiopathy disorders is vast, and needs a great clinical skill to find the origin, especially in patients with systemic lupus erythematosus, in whom it is necessary to consider: associated thrombotic thrombocytopenic purpura, antiphospholipid syndrome, generally of the catastrophic type; localised microangiopathy, or malignant hypertension.
Objective: Using the results reported in the literature, the aim of this article is to describe the frequency, causes and clinical features of thrombotic microangiopathy in systemic lupus erythematosus.
Methods: Structured non-systematic review of the literature.
Results: The review included a total of 51 articles (42 from database searches and 9 referenced in these) on the previously mentioned variables, were included.

Anemia hemolítica microangiopática en lupus eritematoso sistémico: revisión narrativa de la literatura

Palabras clave:
Lupus eritematoso sistémico
Lupus
Púrpura trombocitopénica trombótica

RESUMEN

Introducción: El espectro clínico de los trastornos microangiopáticos es muy amplio y se necesita de una gran habilidad clínica para determinar el origen, especialmente en el paciente con lupus eritematoso sistémico, en quien no solo se debe considerar púrpura trombocitopénica trombótica asociada, sino también: síndrome antifosfolípido; generalmente del tipo catastrófico; microangiopatía localizada o hipertensión maligna.
Objetivo: Describir, de acuerdo con lo reportado en la literatura; la frecuencia, las causas y las

☆Please cite this article as: Coronel Restrepo N, Muñoz-Grajales C, Velásquez CJ, Márquez J, Pinto LF. Anemia hemolítica microangiopática en lupus eritematoso sistémico: revisión narrativa de la literatura. 2015. http://dx.doi.org/10.1016/j.rcreu.2015.05.004

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Anemia hemolítica microangiopática

características clínicas de la microangiopatía trombótica en lupus eritematoso sistémico.
Métodos: Revisión estructurada no sistemática de la literatura.
Resultados: Se incluyeron 51 artículos (42 provenientes de la búsqueda en bases de datos y 9 referenciados en estos) para la revisión de los aspectos de interés mencionados.

Introduction

Thrombotic microangiopathy is characterized by the development of hyaline microthrombi (mostly composed of agglutinated platelets) along the arterioles and capillaries[1]; the term thrombotic microangiopathic anemia[2] makes reference to the presence of hemolytic anemia accompanied by fragmented red blood cells (schistocytes) in the context of a thrombotic microangiopathy.

In patients with SLE, thrombotic microangiopathy may be due to associated thrombotic thrombocytopenic purpura (TTP), antiphospholipid syndrome (APS), usually of the catastrophic type; localized microangiopathy or malignant hypertension.[3,4]

When the thrombotic microangiopathy occurs in the context of systemic lupus erythematosus (SLE), the mortality is higher, compared with those patients with idiopathic TTP.[5]

Methodology

It was conducted a narrative non-systematic review of the literature in English and Spanish languages in the databases: Pubmed, Embase and Lilacs, which would allow answering the following question: in patients with SLE, which are the frequency, the clinical characteristics and the underlying pathophysiologic mechanism of acquired TTP or microangiopathic hemolytic anemia (MAHA)?

The search in Pubmed was developed with the following terms and descriptors: ("Lupus Erythematosus, Systemic" [Mesh]) AND "Purpura, Thrombotic Thrombocytopenic" [Mesh]) OR ("Lupus Erythematosus, Systemic" [Mesh]) AND "Anemia, hemolytic" [Mesh], finding 661 articles, 104 of them published in the last 10 years. It was conducted a search in Embase with similar methodology, without finding articles different to those already cited in Pubmed; 6 articles were found in Lilacs using the search: (lupus eritematoso sistémico) and (púrpura trombocitopénica trombótica); (lupus eritematoso sistémico) and (anemia hemolítica microangiopática) in Spanish language.

The following words were also used in English: lupus; thrombocytopenic; microangiopathic hemolytic anemia; thrombotic microangiopathies; thrombotic microangiopathy; microangiopathy; and in Spanish: lupus; microagiopatía; anemia hemolítica microangiopática.

The summary of each article was read, and the articles related to the questions of interest were selected; the writings referenced in the articles resulting of the search were also reviewed.

Results

A total of 51 articles were included (42 from the search in databases and 9 referenced in these). A review of the aspects of interest mentioned in the methodology will be made below.

General Concepts

In some cases the thrombotic microangiopathy is not due to the deficit of ADAMTS 13 (this deficit may be due to anti-ADAMTS 13 antibodies or to a congenital deficiency, as it will be explained later), but to a condition that induces vascular damage, such as APS, infection with the human immunodeficiency virus, hemolytic uremic syndrome, malignant hypertension, sepsis, disseminated intravascular coagulation, advanced malignant disease or some chemotherapy drugs.[6]

Thus, MAHA in patients with SLE is not always due to TTP.[3,4]

Some authors suggest that when non-immune MAHA (characterized by reticulocytosis, schistocytes and negative direct Coombs test) is observed in the context of SLE, in the absence of a deficit of ADAMTS 13, it should be preferred the term associated AHMA rather than TTP,[7] reserving the latter for the cases of deficit of ADAMTS 13.

Microthrombi (localized microangiopathy) have been described in biopsies from patients with lupus nephritis without TTP and without APS, some of these patients may have microangiopathic hemolysis (because of the event in glomerular capillaries) and neurological alterations due to uncontrolled hypertension being, then, another differential diagnosis to be considered in the patient with SLE, renal deterioration and MAHA.[7]

Thrombotic Thrombocytopenic Purpura: Physiopathological Aspects

Physiologically, from the Weibel-Palade bodies and the alpha granules, located in the endothelial cells and the megakaryocytes, respectively, there is a constitutive release of von Willebrand Factor (vWF), but in the cases of endothelial activation (injury and inflammation) there is a great release upon demand.[4]

The vWF contains several binding sites for different ligands, including the A2 domain where a metalloprotease known as ADAMTS 13 (A Disintegrin And Metalloprotease with Thrombospondin-1 repeats) will act.

When the vWF is released, it has a globular (folded) conformation that will make the A1 (the binding site of GPIbα)

and A2 domains to be partially hidden and the A3 domain (binding site to collagen) to be exposed. As the vWF, in the globular form, passes through the microcirculation, it changes into a filamentous conformation, being exposed the A1 domains, thus having the ability to capture the circulating platelets. In turn, it expresses the A2 domain, facilitating the interaction with ADAMTS 13, exerting a proteolytic intrinsic control.[4]

The ADAMTS 13 (180 kDa) is free in the plasma and there is a small proportion bound to the vWF; it exerts the proteolytic function of vWF in 3 moments[4]: after the constitutional secretion from the Weibel-Palade bodies controlling the release of large multimers into the circulation; in microcirculation, where bound to its substrate converts the vWF multimers in dimers (with less hemostatic potency); and when there is endothelial disruption and the coagulation cascade is activated, limiting the formation of the platelet clot when it still has not been consolidated by thrombin or fibrin.[4]

Today it is known that the activity of ADAMTS 13 can be affected by mutations in the gene that encodes its structure and function (hereditary forms of TTP) or by autoantibodies that inhibit its function (acquired forms of TTP).[3]

Some General Aspects of Thrombotic Thrombocytopenic Purpura

TTP is a rare disease (3.7 cases per million people each year; in the United States of America).[8] But some populations are more susceptible to develop it, including the patients with SLE (1 to 4%).[9]

It is a fatal disease if treatment is not commenced promptly; and almost 60% of those who survive suffer a relapse.[10] As mentioned previously, two forms are known, one congenital, characterized by mutations in the gene that encodes the ADAMTS 13 (there have been described heterozygous forms that are asymptomatic, considering that both alleles must be affected to cause a severe deficit of the enzyme)[3]; and another idiopathic acute or acquired, that is characterized by being mediated by autoimmunity: enzyme inhibitor antibodies against the cysteine-rich domains and the C-terminal domain have been discovered. Usually, these antibodies are of the isotype IgG and less frequently IgM or IgA.[3]

From the clinical viewpoint, TTP is a syndrome characterized by the pentad of MAHA, thrombocytopenia, fever, fluctuating neurological deficit and renal disease, but up to 35% of patients do not have neurological symptoms, or renal involvement and fever are not present[3]; due to the high mortality, in the absence of treatment, it should be suspected with the mere presence of thrombocytopenia and MAHA and therapy should be initiated in order to prevent serious outcomes.[11]

The first case was described by Dr. Moschcowitz in 1924,[12] but only until 1982 Dr. Joel Moake[13] discovered that the plasma of patients with continuous recurrent TTP had a great amount of ultralong multimers of vWF. In 1996, the work of Furlan and Tsai[14,15] allowed to establish that there was a protease with catalytic activity over the vWF and that it was absent in the sera of patients with TPP.[16-18]

t has been defined as a severe deficiency of ADAMTS 13 an activity < 5%, finding that has been reported more frequently in patients with hereditary forms. In transgenic murine models it has been observed that the deficit of ADAMTS 13 is a risk factor for the development of TTP and not necessarily a direct triggering factor, suggesting that the exposure to an additional prothrombotic stimulus is necessary for the development of the disease.[19,20]

Severe deficiencies of ADAMTS 13 are found only in three-quarters of patients with acquired TTP.[21]

Under normal conditions the ADAMTS 13 does not have a natural inhibitor and is likely that its activity is diminished by the free hemoglobin, the proteolytic degradation by plasmin and thrombin or by mutations in the complement factor H. In 2007, Tachil[22] said that the states of severe intravascular hemolysis generate a saturation of the protective processes (haptoglobin and monocyte/macrophage system), favoring the free hemoglobin to be able to bind strongly to nitric oxide, altering the ability of vasoregulation, mainly in the brain, and this situation would explain the neurological fluctuation characteristic of the patients with TTP and, in addition, non-specific symptoms such as abdominal pain, dysphagia and nausea.[22] It is probable that other products of hemolytic processes might have an inhibitory effect on the ADAMTS 13.[22]

All the above could reveal why plasmapheresis is useful in patients with clinical signs of thrombotic microangiopathy with normal levels of ADAMTS 13 –possibly by removing the products of hemolysis and administering additional nitric oxide.[22]

Microangiopathic Hemolitic Anemia Associated to Systemic Lupus Erythematosus

Its association with SLE was recognized in the medical literature in 1939 when the first case was described by Gitlow and Goldmark.[23,24] With respect to the underlying pathophysiology, as in the majority of series and case reports, a parallel course in the activity of SLE and MAHA is observed and the patients with TTP in the context of SLE, who are refractory to plasma exchanges, respond to the use of cytotoxic agents, it has been suggested an event mediated by antibodies,[24] but even though antibodies IgG inhibitors of ADAMTS 13 were discovered initially in these patients, subsequent studies such as the one conducted by Pier Manucci et al.[25]; which evaluated the levels of protease and vWF antigen in patients with autoimmune diseases (SLE and systemic sclerosis), and anti-ADAMTS 13 were sought in those who had levels of ADAMTS 13 < 40%; demonstrated that while the levels of ADAMTS 13 were significantly lower in patients with SLE ($p = 0.013$) and with systemic sclerosis ($p = 0.0002$) compared with healthy controls, there were no anti-ADAMTS 13 in the patients with low levels of protease; allowing to consider that there may exist more than one mechanism involved in the development of MAHA in the patient with SLE (it is not exclusively due to anti-ADAMTS 13 antibodies).

That is how 3 subgroups of patients with TPP or MAHA are recognized in SLE: those with severe deficiency of ADAMTS 13 due to IgG inhibitor antibodies; those with moderate deficiency

with or without inhibitor antibodies and those who have normal or subnormal levels without inhibitor antibodies.[25,26]

For this reason, oxidation of vWF, endothelial activation and injury, defects in fibrinolysis (TPa) and vasculitis, have been suggested as alternative mechanisms of thrombotic microangiopathy in SLE.[26]

It is important to mention that between 13% and 18% of patients with SLE or APS may have anti-ADAMTS 13 antibodies without manifestations of MAHA[27] and some authors have observed the presence of ANA and anti-DNA in patients with idiopathic TTP without any characteristic of SLE (71% and 9.7%, respectively); is related with a greater deficiency of ADAMTS 13.[27]

Prognostic Considerations

Already since 2004[28] it had been determined how those patients with TTP and absence of ADAMTS 13 (severe deficiency) used to have a good response to conventional treatments and those with ADAMTS 13 present had a gloomier prognosis, with poor response to plasmapheresis and a mortality of 60% to 90%. The latter group is characteristic of patients with allogeneic bone marrow transplant and patients with SLE.

In a study conducted in Korea, in which were found as risk factors for the development of TTP in patients with SLE: SLEDAI > 10 and the coexistence of nephritis, a mortality near to 46% is described when there is concomitance of SLE and TTP, especially when infection occurred (independent risk factor for mortality).[24] Other studies have also found infectious processes as a cause of mortality.[29]

As risk factors for developing TTP in SLE have been described: high disease activity, presence of anti-Sm, renal affection and being young (between 30 and 34 years of age).[3,24]

Clinical Considerations

In 2008 at the University of Louisiana[30] it was carried out a retrospective analysis of 114 patients with exacerbations of SLE, comparing those who had MAHA with those who did not. All of them had MAHA and thrombocytopenia, and only one exhibited the classic pentad. Remarkably and with statistical significance, the patients with microangiopathy had a higher SLEDAI score (15.3 vs. 6.4 p = < 0.0006). In the same way, in a hospital in Singapore, between January 2003 and December 2007, it was compared the behavior of patients with TTP, with or without SLE,[31] and it was found that the average duration from the first symptom of TTP until the diagnosis of MAHA was longer in patients with TTP associated with SLE (19.5 days vs. 7.7 days), who, in addition, were younger (34.5 years vs. 50.4 years).

Lansigan[9] noted that in 73% of cases TTP appears after the onset of SLE and the results of Musio,[32] in 40 patients with TTP, demonstrated that 15% of patients develop SLE after the diagnosis of TTP and 12% concomitantly.

Jiang et al.,[33] conducted a work in which they analyzed the patients with TTP associated with SLE from 1999 until 2011. 105 patients were included, and those who survived (92 patients) where compared with those who did not (13 patients). A diagnosis of TTP was made in those who had MAHA and thrombocytopenia not explained by other causes, associated at least to one of the following: fever, neurological deficit or renal dysfunction. In this work in 50.5% of patients the onset of SLE was preceded by TTP. 100% of patients who died had neurological symptoms compared with 72.8% of the group who survived (p = 0.035). A renal biopsy was taken only in 52 patients, revealing thrombotic microangiopathy in 5.8%. Renal thrombotic microangiopathy appeared more frequently in the group who died (p = 0.042). The presence of antiphospholipid antibodies (33.3 vs. 29.7%), the severe deficit of ADAMTS 13 < 5% (66.7 vs. 40.6%) and anti-ADAMTS 13 (100 vs. 91.7%), occurred more frequently in the group that did not survive, but were not statistically significant.

When TTP is associated with SLE, the mortality is higher compared with those patients with idiopathic TTP; Dr. Pagalavan Letchumanan et al., in 2009,[31] in a population of Singapore that included 10 patients with idiopathic TTP and 8 patients with TTP associated with SLE, found that the mortality for the idiopathic form was 50% (95% CI 19%, 81%) and for the secondary TTP of 62.5% (95% CI 29%, 96%). The authors considered that the higher mortality was due to: 1) presence of 2 concomitant fatal diseases, 2) the multisystemic compromise of SLE has a spectrum of clinical presentation similar to TTP, delaying the diagnosis and institution of timely treatment, and 3) the patients with secondary TTP are often refractory to plasmapheresis.

Given the high mortality, is important to be alert in patients with SLE that have hemolytic anemia with negative direct Coombs test, looking for the presence of schistocytes that suggest microangiopathy.[34]

Treatment

Plasma exchanges reduce mortality in TTP (it changes from about 90% to 20%), for this reason is necessary their implementation in all patients, even in patients with SLE.[3]

Until 2001, for the management of MAHA in SLE, some authors had used steroids with plasma exchanges or steroids with cytotoxic agents (cyclophosphamide or vincristine) and plasma exchanges (concomitantly, or first the exchanges and then the cytotoxic agents if there was refractoriness).[24,35-45] In 2002, Vasoo et al., compared the effectiveness of these two therapeutic strategies, finding a mortality of 33% and 25%, respectively, being the leading causes of death the refractory TTP and the infections,[24] and the latter were more frequent in those patients who used cytotoxic agents, therefore, the use of cytotoxic agents was suggested only if there was refractoriness to plasma exchanges or if the concomitant lupus manifestation (e.g. lupus nephritis) required it; favoring the use of cyclophosphamide over vincristine, because of having more experience of use in lupus patients.[24]

However, subsequent observations have demonstrated that patients with TTP and SLE are often refractory to plasma exchanges: while the complete remission in idiopathic TTP is achieved in 50% of patients in 16.8 days of plasma exchanges, in TTP associated with SLE it only gets to be of 37.5% after 31.3

days of use of plasmapheresis,[46] and therefore, currently is deemed necessary the use of steroids, plasma exchanges and cyclophosphamide for the treatment of TTP associated to SLE. Other immunossuppressants described in TTP associated with SLE have been: cyclosporine, azathioprine, mycophenolate, immunoglobulin and immunoabsoption.[7,46,47]

More recently, and extrapolating the favorable effect on idiopathic TTP, there have been described cases with satisfactory response to rituximab in patients with TTP and SLE refractory to plasmapheresis,[46-50] being especially useful to reduce the number of days of plasma exchanges required to achieve stability and remission and to decrease the number of relapses.[46,48-51]

Conclusions

The clinical spectrum of microangiopathic disorders is very broad; a great clinical ability is needed to diagnose them, especially in the patient with SLE.

In a patient with SLE and thrombotic microangiopathy not only should be considered an associated TTP, it also should be ruled out an associated APS syndrome, usually of the catastrophic type, localized microangiopathy and malignant hypertension.

The presence of 3 subgroups of patients with TTP or MAHA in SLE: those who have severe deficiency of ADAMTS 13 due to IgG inhibitor antibodies; those with moderate deficiency with or without inhibitor antibodies, and those who have normal or subnormal levels without inhibitor antibodies; suggests that there is more than one pathophysiological mechanism in the development of MAHA in SLE.

When the TTP is associated to SLE, the mortality is higher and the response to plasma exchanges is lower. Since the classical pentad of TTP is usually absent in SLE, it is mandatory to suspect it and establish a timely treatment, with the mere presence of MAHA and thrombocytopenia.

The current treatment consists of systemic steroids, plasma exchanges and immunossuppressants (especially cyclophosphamide); rituximab has been useful in cases which are refractory to plasma exchanges and it shortens the number of days of plasma exchanges to achieve remission.

Conflict of Interest

The authors declare that they have no conflict of interest.

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