Acquired Inhibitors of Coagulation in a Patient With Systemic Lupus Erythematosus and Antiphospholipid Antibodies: Response to Rituximab

Enrique Ortiz Jiménez,a Sergio Loera Fragoso,a and Marina Rull Gabayetb

aHospital General de Durango, Durango, Mexico
bInstituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Distrito Federal, Mexico

Hematologic signs of systemic lupus erythematosus are diverse (SLE). Although a delayed coagulation time is anti-phospholipid antibody related, thrombotic events are the usual clinical manifestation. Spontaneous appearance of circulating anticoagulant in the absence of a previous coagulation disorder is secondary to the development of antibodies to factors II, V, VIII, IX, XI, XII, vonWillebrand, and other membrane glucoproteins, all of them uncommon causes (1 case per million persons per year) of life threatening coagulopathies. We report a case of SLE and antiphospholipid antibodies in a woman with a hemorrhagic syndrome, probably caused by multiple antibodies to coagulation factors, unresponsive to steroids and high-dose immunsuppressive therapy and a favorable response to rituximab.

Key words: Systemic lupus erythematosus. Acquired coagulation inhibitors. Lupus anticoagulants. Rituximab.

Inhibidores adquiridos de la coagulación en una paciente con lupus eritematoso sistémico y anticuerpos antifosfolípídicos: respuesta a rituximab

Las manifestaciones hematológicas de los pacientes con lupus eritematoso sistémico (LES) son diversas. Aunque el desarrollo de anticuerpos antifosfolípídicos se asocia con una prolongación in vitro de los tiempos de coagulación, las manifestaciones clínicas suelen ser trombóticas. Los anticoagulantes circulantes que aparecen en pacientes sin anormalías previas de la coagulación son consecuencia del desarrollo de autoanticuerpos contra los factores II, V, VII, VIII y IX, XI, XII, factor de Von Willebrand u otras glucoproteínas de membrana. Todos ellos condicionan coagulopatías poco comunes, 1 caso por millón de personas por año, y que pueden comprometer seriamente la vida de los pacientes. Presentamos el caso de una mujer con LES y anticuerpos antifosfolípídicos, que presentó síndrome de Evans, como primera manifestación, y posteriormente desarrolló un síndrome hemorrágico, presumiblemente por anticuerpos contra múltiples factores de la cascada de coagulación, sin respuesta a dosis altas de esteroides e inmunosupresores, que finalmente respondió a rituximab.


Introduction

Acquired inhibitors of coagulation in patients with no previous abnormalities in the coagulation process are the result of the spontaneous development of autoantibodies directed against factors of the coagulation cascade or other membrane glucoproteins.1,2 Although in approximately 50% of cases the etiology is unknown, conditions that are frequently associated with the development of acquired inhibitors of coagulation are puerperium, autoimmune diseases, drug reactions, cancer, and infections.3 With the objective of reducing the titer of antibodies against coagulation factors, different treatment strategies such as plasmapheresis, immunoglobulin immunoabsorption, steroids, and immunosuppressants, such as cyclophosphamide and azathioprine, have been employed.4 We describe the case of a woman with SLE and antiphospholipid antibodies who presented Evans syndrome and then developed a severe hemorrhage, associated to a reduction in the activity of multiple coagulation factors, without a response to plasma infusions, high-dose steroids and azathioprine, and finally responded to rituximab.
Clinical Case

A 26-year-old woman, without any important history, was hospitalized in the Hospital General de Durango for malaise, fever, arthritis, spontaneous ecchymoses, gum, and nose bleeding. Her blood count showed hemoglobin 10.7 g/dL, leukocytes 1300/µL, and thrombocytes 69 000/µL, with an elevated reticulocyte count and an increase in the numbers of indirect bilirubin and lactate dehydrogenase (LDH), as well as a positive Coombs test, positive antinuclear antibodies, low C3 and CH50, proteinuria, positive anticardiolipin antibodies, both IgG and IgM (36 U and 54 U GPL and MPL, respectively), and a false positive VDLR. On that occasion she was treated with pulse methylprednisolone in 3 doses of 1 g followed by a 1 mg/kg/day daily dose of prednisone, with a normalization in the hemoglobin levels and the platelet count, as well as improvement in symptoms, with the exception of the hemorrhage and an increase in the coagulation time (PTT, 47%/29%) which did not correct with plasma. Because of this, azathioprine and chloroquine were added, without a response after 4 months of treatment. A determination of the plasma activity of the coagulation factors showed a descent in the activity of all of them. Considering the poor response to the therapy employed up until that moment, we opted for the use of rituximab, 2 doses of 1 g with a 2 week interval between administrations. Three weeks after the second dose, the patient reported the hemorrhage ceasing, with the blood count and the PTT resulting normal and a new determination of the different coagulation factors (Figure), showed a clear normalization in the activity of the coagulation factors which persisted up to 2 months, with clinical improvement of the rest of the symptoms such as joint pain and photosensitivity.

Discussion

Systemic lupus erythematosus is an autoimmune disease that is characterized by the presence of antibodies directed against multiple autoantigens. There are multiple hematologic manifestations of lupus, described classically as hemolytic anemia, thrombocytopenia, leukopenia, and lymphopenia. On the other hand, in up to a quarter of patients with lupus it is possible to detect antiphospholipid antibodies, basically anticardiolipin antibodies, lupus anticoagulant and anti-β2 GP-1, although the importance of other autoantibodies in the physiopathology of this syndrome has recently been described, such antibodies against phosphatidylcholine and annexin V, which unfortunately were not determined in this patient; however, the presence of these has also been associated to the development of predominantly thrombotic events, not hemorrhage. The hemorrhagic manifestations of lupus are infrequent and have been attributed to the development of antiprothrombin antibodies. The clinical case we have presented is interesting, because acquired inhibitors of coagulation or circulating anticoagulants represent an infrequent entity with hemophilia A being the most frequent of all of them with an incidence of 0.2 to 1 case per million persons per year and the coexistence of multiple coagulation inhibitors has not been described. Although in this case it was not possible to confirm the presence of inhibitor antibodies, the reduction in the percentage of activity of the different factors with normal controls is an indirect indicator of its presence. An alternative to them should be an insufficient production or an increase in the consumption of coagulation factors, something that can be seen in liver failure or disseminated intravascular coagulation, which was ruled out in the case of this patient.

With respect to treatment, there are no concrete management recommendations and the current information is derived from case reports. Plasmapheresis, immunoglobulin immunoabsorption, steroids, and immunosuppressants have been employed as treatment alternatives, with the objective of reducing the antibody titers and whose most serious side effects are consequences of generalized immunosuppression. Anti-CD20 therapy has been explored in multiple autoimmune diseases, among them SLE and rheumatoid arthritis, and there are case reports of acquired hemophilia treated with rituximab, achieving good results. Therefore, it is attractive to assume that anti-CD20 therapy is an alternative of more limited immunosuppression and could represent a treatment option in patients with acquired deficiencies.
inhibitors of coagulation, resistant to conventional immunosuppressants or in whom their use is not recommended.

References