

Case report

Ecilizumab as a therapeutic option for patients with scleroderma renal crisis associated with hemolytic uremic syndrome[☆]



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ABSTRACT

Scleroderma renal crisis (SRC) is a rare manifestation of systemic sclerosis (SSc), presented as hypertension of new onset, worsening and/or acceleration of chronic hypertension, or rapid deterioration of renal function, often accompanied by signs of microangiopathic haemolysis. It is rarely associated with haemolytic uraemic syndrome, and there is only one similar case reported in the literature. The case is presented here of a 36-year-old woman on treatment for ES with global, pulsatile and intense headache, clonic tonic convulsions, high blood pressure levels, acute renal failure, and persistent non-autoimmune haemolysis. The evaluation of ADAMTS13 showed 60.6% of activity. The genetic study to search for mutations predisposing to atypical haemolytic uraemic syndrome (aHUS) revealed a homozygous variant in ADAMTS13 gene, c.3287G>A (p.Arg1096His), Ecilizumab was started, with an improvement being observed in a short time in the haemolysis, renal function, and clinical status, with some notable and unexpected beneficial effects on SSc.

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Ecilizumab como opción terapéutica en paciente con crisis renal esclerodérmica asociada a síndrome hemolítico urémico

RESUMEN

La crisis renal esclerodérmica (CRS) es una manifestación rara de la esclerosis sistémica (ES), se presenta como hipertensión arterial de nuevo inicio, empeoramiento o aceleración de la hipertensión arterial crónica o rápido deterioro de la función renal,

Palabras clave:

Crisis renal esclerodérmica

Síndrome hemolítico urémico

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Eculizumab
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frecuentemente acompañada de signos de hemólisis microangiopática. Su relación con el síndrome hemolítico urémico es infrecuente, existiendo tan solo un caso similar reportado en la literatura. Presentamos el caso de una mujer de 36 años en tratamiento para ES con cefalea global, pulsátil e intensa, convulsión tónico clónica, cifras de presión arterial altas, falla renal aguda y hemólisis no autoinmune persistente. La evaluación de ADAMTS13 reveló 60,6% de actividad, el estudio genético para búsqueda de mutaciones predisponentes para síndrome hemolítico urémico atípico (SHUa) revela variante homocigota en el gen ADAMTS13, c.3287G>A (p.Arg1096His), se inició eculizumab observándose en poco tiempo mejoría de la hemólisis, función renal y estado clínico con algunos efectos benéficos notorios e inesperados sobre la ES.

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease involving multiple organs and characterized by excessive accumulation of collagen, autoimmunity, vascular hyper-reactivity and obliterating microvascular phenomena. The vascular injury may manifest as Raynaud's phenomenon, digital ischemia, pulmonary hypertension, or scleroderma renal crisis (SRC). It is rarely associated with hemolytic-uremic syndrome, with only one case being reported in the literature.^{1,2} SCR is a rare manifestation of SSc and presents as new-onset hypertension, worsening or acceleration of chronic hypertension, or rapidly declining kidney function, usually accompanied by signs of microangiopathic hemolysis.³ Nowadays, SCR develops in around 5%–10% of the patients, mostly those with diffuse systemic sclerosis.⁴

This article discusses a case of acute kidney failure with thrombotic microangiopathy (TMA), microangiopathic hemolytic anemia, in a patient with underlying systemic lupus erythematosus and SSc. What makes this case so interesting is that the microangiopathic hemolysis was resolved with anti-C5 monoclonal antibodies therapy (eculizumab).

Case discussion

A 36-year old female was admitted to the emergency department after 14 h with global, pulsating, and intense headache, followed by generalized tonic-clonic seizures and blood pressure of 195/120 mmHg. The initial assessment revealed a heart rate (HR) of 100 bpm, respiratory rate (RR) of 25 breaths/minute, temperature of 36.2 °C, pulse oximetry 91% with FiO₂ 0.21, time and place disorientation, with no focal neurologic deficit, no meningeal signs, and event amnesia.

The physical examination reported microstomy and sclerodactyly, with no other relevant findings. The patient had been diagnosed in December 2015 with overlap syndrome with probable systemic lupus erythematosus, supported by episodes of recurrent serositis (discrete pericardial and pleural effusion), leucopenia, homogeneous pattern antinuclear antibodies (ANA) titer 1:640 and complement consumption in addition to a sclerosis component documented by sclerodactyly, non-specific interstitial pneumonia (NSIP),

microstomy and anti-Scl 70 positive titer 108.6 (diffuse form of SSc). The patient was being treated with chloroquine 250 mg/day and prednisone 1 mg/kg/day (60 mg/day), methotrexate 15 mg/week as steroid-sparing agent, and colchicine.

The laboratory tests at admission included CBC with 15,520 leukocytes, 13,270 neutrophils, 1580 lymphocytes, hemoglobin 9.5 g/dl, hematocrit 30%, mean corpuscular volume 97 fl, erythrocyte distribution width 18.3%, 100,000 platelets, creatinine 6.7 mg/dl, BUN 78.9 mg/dl, potassium 4.3 mEq/l, sodium 132 mEq/l, chlorine 102 mmol/l, calcium 8.9 mg/dl, total bilirubin 1.0 mg/dl, normal direct and indirect bilirubin, GOT 33 U/l, GPT 15 U/l, alkaline phosphatase 57.4 U/l, glycemia 89 mg/dl, C-reactive protein 125.8 mg/l, peripheral blood smear with normal leukocyte count, normal white blood cell morphology, 89% neutrophils, 5% lymphocytes, 6% monocytes, erythrocyte morphology with anisocytosis: microcytes +, polychromatophilia: poikilocytes +, schistocytes ++, decreased manual count platelets 99,000/mm³, reticulocytes 6.5%, lactic dehydrogenase (LDH) 663 U/l, negative direct Coombs, normal urinalysis, no proteinuria, no active sediment, normal arterial gases, plain head CT with cortical-subcortical hypodensity, some bilateral occipital lacunae, transthoracic ultrasound indicating pericardial effusion with 350 mL, intact and normal function valves, depressed global contractility with ejection fraction of 30%. The patient was diagnosed with reversible posterior encephalopathy, hypertensive emergency, thrombotic thrombocytopenic purpura-like SRC and TMA vs. atypical hemolytic-uremic syndrome (aHUS). The patient was treated with IV labetalol, the prednisone dose was lowered to 15 mg/day, oral nifedipine, in addition to a prescription for 5 plasmapheresis sessions—1.5 L/day. The clinical evolution was unfavorable, although the encephalopathy was reversed with complete neurological recovery, and so labetalol could be removed with blood pressure control. The skin involvement progressed rapidly to overt scleroderma with a Rodnan score of 22 and Raynaud phenomenon, capillaroscopy with abnormal length, abnormal diameter, tortuosity, angiogenesis +, megacapillaries +, findings compatible with late stage scleroderma. Additionally, the patient developed kidney injury progressing to anuria and required starting renal support therapy with hemodialysis. The pulmonary antifibrotic management was adjusted to mofetil 3 g/day; additionally, the patient con-

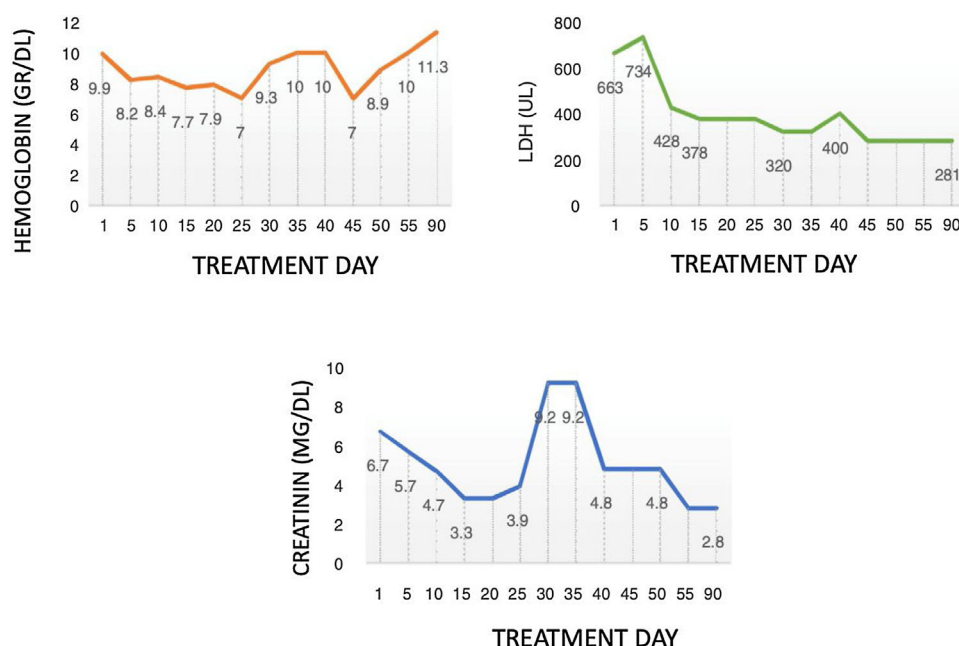


Fig. 1 – Levels of Hemoglobin, creatinine and LDH during treatment.

tinued to present anemia, LDH elevation, low haptoglobin, peripheral blood schistocytes; anti-RNP, anti-SM, anti-RO, anti-LA, C3, C4, P-ANCA, C-ANCA, HBV, HCV, anticardiolipin IgG, IgM, antiphospholipid IgG, IgM, anti-nucleosome were negative.

ADAMTS13: 60.6% activity. The genetic study to identify mutations predisposing for aHUS revealed a homozygotic variant of the ADAMTS13 gene, c.3287G>A (p.Arg1096His) found in a preserved nucleotide and poorly preserved amino acids position with minor physicochemical differences among the exchanged amino acids (Alamut v.2.7.1), C3, CD46, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR5, CFI, DGKE, PIGA, THBD had no pathological variations, CFH, CFHR1, CFHR2, CFHR3, CFHR5 had no deletions or duplicates.

The kidney ultrasound showed increased echogenicity of the renal cortex. An attempt was made to show renal thrombosis but the kidney biopsy was inconclusive because the sample was insufficient. In view of persistent worsening, the decision was made to immunize the patient against meningococci and pneumococci and to treat with eculizumab. Following the induction dose, the hemoglobin levels stabilized, the hemolysis was controlled and LDH decreased, so the patient could be discharged 2 weeks after the induction (Fig. 1). The patient experienced a constitutional paradoxical adverse effect with the administration of mycophenolate, which led to the discontinuation of the drug and the patient did not receive any other antifibrotic agent. During the control visit 3 months later, the blood pressure levels had normalized and antihypertensive therapy was removed; only eculizumab was continued. Surprisingly, the patient was stable and the skin involvement was reversed, with a new Rodnan score of 14; the Reynaud phenomenon also improved, in addition to the cardiovascular recovery shown in a control transthoracic ECG with improved overall contractility, resolution of the pericardial effusion, ejection fraction of 64% and improved dyspnea. The control

high resolution chest CT showed no variations as compared to the previous CT.

Discussion

SSc presents in a female-to-male ratio of 3–8:1 and has a peak incidence around 45 and 64 years old. Apparently, there is a higher frequency of the disease among black women. The criteria to consider a SRC include severe hypertension, rapidly progressive acute renal failure, microangiopathic hemolysis and thrombocytopenia (<100,000 platelets). The consensus for diagnostic criteria in 2016 were: hypertension defined as a blood pressure >150/85 mmHg, systolic blood pressure elevation of >20 mmHg as compared to the baseline in two measurements in 24 h. The associated manifestations were defined as a 50% creatinine elevation over the baseline or an absolute increase of 0.3 mg/dl (26.5 μ mol/l), proteinuria >2+, hematuria >1+ per strip or >10 red blood cells per high power field.⁵ High blood pressure is present in up to 90% of the patients; the most frequent clinical findings are head ache, blurred vision and signs of encephalopathy.

Other manifestations include: ischemic stroke, hypertensive retinopathy, heart failure, pulmonary edema, pericarditis, cardiac arrhythmias, oliguria and general malaise. Intracerebral hemorrhage is a rare occurrence. The routine use of angiotensin converting enzyme inhibitors (ACE inhibitors) has significantly improved the outcomes over the past few years. However, SRC is still a devastating manifestation of the disease and the functional outcomes, as well as the survival rates are poor; the best case series have reported survival rates of 70.9% at one year, 66.6% at 2 years, 60% at 5 years, and 41.9% at 10 years.^{6,7} Some of the risk factors identified for the development of SRC include: anemia, myocarditis, heart failure, cardiac arrhythmias, positive anti-SCL70, the use of steroids

(prednisone more than 15 mg/day or its equivalent) up to 6 months before the onset of the condition. There have been similar reports with the use of cyclosporine. The most common laboratory findings are: creatinine elevation that may persist for several days, even after controlling the high blood pressure; proteinuria within 0.5–2.5 g/l, microscopic hematuria, hemoglobinuria, anemia and thrombocytopenia which account for TMA in 43% of the patients; thrombocytopenia is usually mild to moderate, rarely below 50,000 platelets/mm³ and typically, TMA resolves upon controlling the hypertension. Anti-SCL70 are present in up to 33% of the cases, and anticentromere antibodies in 1%–3% of the cases. The advantage of a renal biopsy is still controversial; certainly it is not essential to make a diagnosis, but it may help to rule out the differential diagnosis and assess the prognosis. If TMA persists, a complex analysis is needed to differentiate TMA from SRC and look for other TMA causes, including: TTP and aHUS. Complement deregulation-mediated TAM involves genetic and acquired mechanisms; the complement cascade is the cornerstone of innate immunity and involves a delicate balance between complement activity and constant control. When this balance is disrupted, aHUS develops and its pathogenesis is the result of a dysregulation of the alternative complement pathway (ACP). The regulators participating in this process are factor H (FH), factor I (FI) and membrane cofactor protein (MCP). Several studies have identified complement gene mutations in up to 60% of patients with aHUS as part of the genetic mechanisms of the syndrome; these mutations usually present with heterozygosity and phenotype penetration in up to 50%. The most frequent mutation of aHUS is FH, identified in 25% of the sporadic cases and in 40% of family cases.

This paper discusses a difficult and complex case of a white, young adult Colombian woman who after almost 2 years of study had been diagnosed with overlap syndrome which progressively changed towards diffuse SSc and developed an episode of hypertensive emergency compatible with SRC based on clinical factors, laboratory findings and history, including: the progression over the first year of the disease, sudden blood pressure elevation, laboratory findings highly suggestive of TMA, and use of high doses of steroids, ruling out other causes for kidney failure.

Whilst the 2016 SRC consensus criteria to define hypertension and kidney failure are arbitrary and are not consistent with the current guidelines for chronic high blood pressure and kidney failure, our patient did not have a history of systemic high blood pressure, and hence this made the diagnosis more feasible. After receiving care, the blood pressure levels were controlled and the neurological symptoms, as well as the cardiopulmonary decline were resolved. However, the TMA persisted and required us to clinically determine how long could this finding persist within the context of SRC. Unfortunately, this fact is unclear and we were unable to identify any medical literature to answer the question. Nevertheless, most reports indicated that by controlling blood pressure within normal levels, the microangiopathic condition should go away. Based on the clinical response observed, the progressive anemia, thrombocytopenia, LDH elevation and persistence of schistocytes we actively looked for differential diagnoses exploring the possibility of TTP or aHUS, as

a priority to establish the survival of the patient. Although most reports suggest that in the presence of TTP, the observed thrombocytopenia is usually more severe and platelets are below 50,000, platelet count is not a real indicator to help differentiate TTP from aHUS, so this parameter alone should not govern the therapeutic decision. In contrast, the level of ADAMTS13 activity is an excellent marker for innate and acquired conditions and may help to differentiate TTP. In our case, the ADAMTS13 activity was evidently above 5% (60.6%), suggesting the presence of aHUS. The genetic study revealed a homozygote variant in the ADAMTS13 gene; as already mentioned, several genes are known to be related to aHUS, and this predisposition is inherited in an autosomal recessive or dominant manner, with incomplete penetrance. Very seldom is inheritance digenic and the occurrence of aHUS varies from childhood to adulthood.⁸ Variants in the ADAMTS13 gene are the cause for familial TTP; however, these variants have also been described by Feng et al.⁹ in patients with aHUS, particularly in combination with another variant (A747V). The functional analyses of these variants reveal the significant difference as compared with a normal recombinant ADAMTS13. This variant is considered a common finding in aSHU patients and its frequency is 0.01288; in other words, 1546 in 120,050 alleles and may rise up to 0.1128 for the Latin population or drop to 0.0034 for the European-American population, and to 0.0023 in African populations.¹⁰ Based on these findings, a genetic predisposition to aHUS may not be confirmed in our patient but there is the likelihood of an increased susceptibility, which has been correlated with a clinical improvement following the administration of anticomplement therapy with eculizumab (C5-targeted monoclonal antibody C5).

Conclusion

This case discussion is intended to show the huge complexity of diagnosing SRC—a rare pathology which may present in subjects with increased sensitivity, as a complement-amplifying condition for the development of aHUS. This leads to a new medical approach involving the advancement and current state-of-the-art knowledge, recognition of clinical patterns, expertise, genetic analysis and the use of new biologics. There are still many unanswered questions with regards to the use of anticomplement therapy, including: how long should the therapy be, risk of meningococcal infection, risk of immune response to the biologic, dose limitations and frequency of therapy, improvement criteria, and in our special case, the incidental finding of a significant clinical improvement of the skin and cardiovascular manifestations of the diffuse SSc, without any additional therapy besides anticomplement management. The question for future research initiatives is then whether it is possible that the complement pathway be the solution for managing SSc.

Conflicts of interest

The authors have no conflict of interest to disclose.

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