

Complement C5-blocking Agent in Refractory Dermatomyositis

To the Editor:

Dermatomyositis (DM) is a rare autoimmune disease that belongs to the group of idiopathic inflammatory myopathies (IIM). The usual treatment of DM was based on steroids, methotrexate, and azathioprine. Intravenous immunoglobulin (IVIG), rituximab (RTX), or other biological treatments recently emerged as steroid-sparing agents¹. About 10% to 30% of patients will develop a refractory or chronic persistent disease², suggesting that alternative treatments should be tested. Here, we report a case of acute refractory DM with concomitant thrombotic microangiopathy (TMA) that improved with the C5-blocking agent eculizumab in the setting of other medications.

According to the French law regarding observational retrospective studies (Jardé Law, 2016), written informed consent to publish the material was obtained from the patient, but approval by a specific ethics board was waived.

A 19-year-old female patient, without medical history or medications, developed moderate arm and limb muscle weakness, Raynaud phenomenon, Gottron papules, mechanic's hand, and edema of limb, arm, and periorbital regions. One month later, she was admitted to the hospital for severe acrocyanosis (Figure 1A–B), and examination showed elevated muscle enzymes [creatinine kinase (CK) 11.243 IU/l, myoglobin 10.152 ng/ml, troponin 7.404 ng/l]. Cardiac magnetic resonance imaging (MRI) showed left ventricle hypertrophy and pericardial effusion suggestive of myocarditis, but breath-related artifacts precluded definitive diagnosis. Capillaroscopy

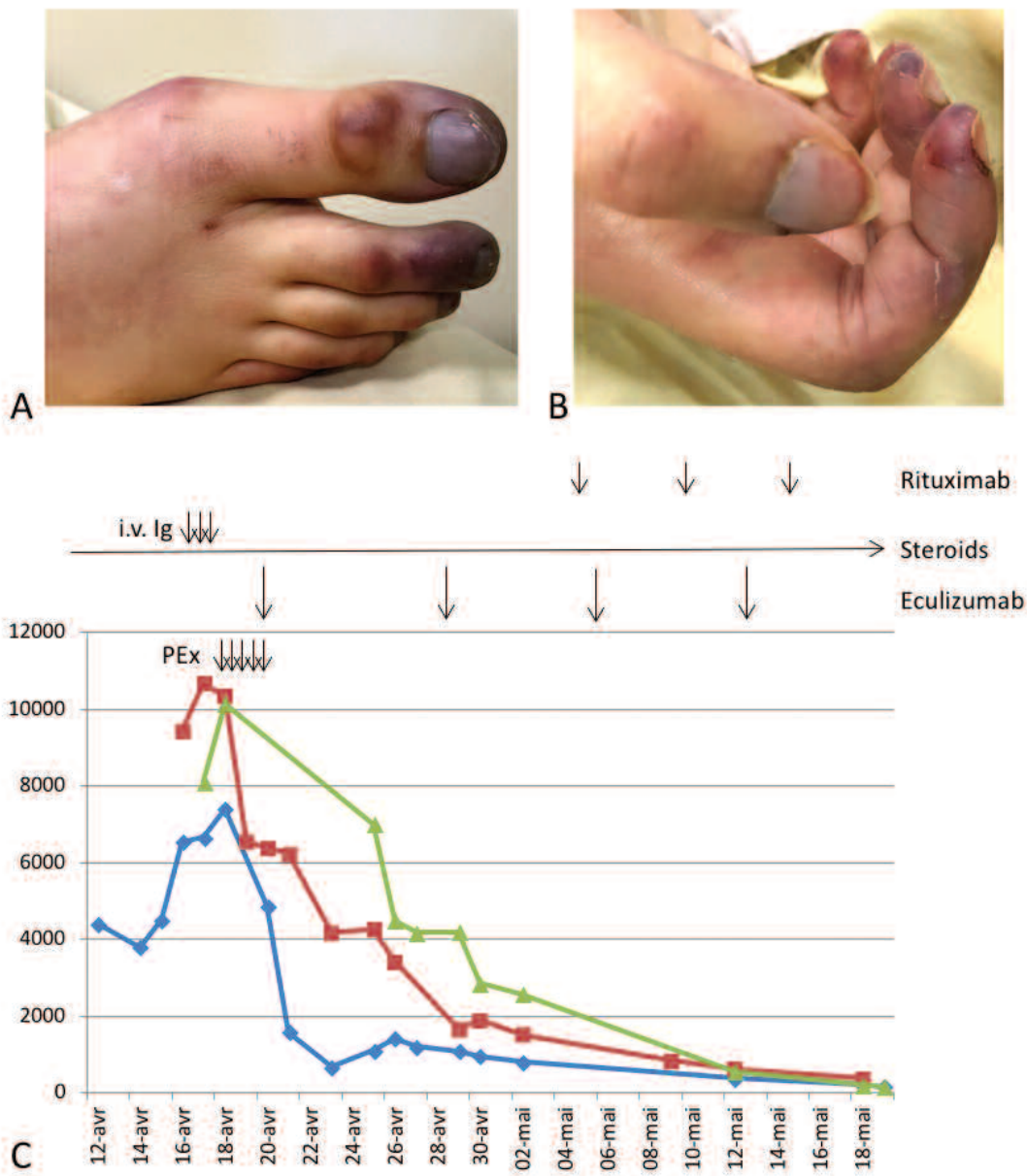


Figure 1. A and B. Severe acrocyanosis of the fingers and toes, with Gottron papules and scleroderma. C. Kinetics of CPK (red; IU/l), myoglobin (green; ng/ml), and troponin (blue; ng/l). IVIg: intravenous immunoglobulins; CPK: creatine phosphokinase; PEx: plasma exchange.

demonstrated abnormal tortuous nailfold capillaries. Immunological tests showed only low serum complement C3/C4 components and increased soluble C5b-9 (Supplementary Table 1, available from the authors on request), but no antinuclear antibodies and myositis-specific autoantibodies. Neuromuscular biopsy showed perivascular and perimysial infiltration of nonnecrotic muscle fibers with CD4+ T cell and CD68+ macrophages, MHC-1 antigen expression close to the inflammatory infiltrates, and focal perifascicular atrophy suggestive of seronegative DM³. At that time, she had arthralgia but no arthritis, dysphagia, or interstitial lung disease. Skin biopsy and muscular MRI were not performed. Diagnosis of DM was retained according to the Bohan and Peter criteria (skin lesions and 3 out of 4 major criteria)⁴. Methylprednisolone (2 mg/kg/day) was started and IVIG was added at Day 3 because of persistent pain and edema of the legs, arms, and face, and elevated CK.

At Day 4, the patient was referred to our intensive care unit (ICU) for acute kidney injury with glomerular presentation (serum creatinine 278 μ mol/l, protein-to-creatinine ratio 2.9 g/g, hematuria, hypertension) and features of TMA (hemolytic anemia, thrombocytopenia, decreased haptoglobin, lactate dehydrogenase increase, and circulating schizocytes). Search for anti-ADAMTS13, anticardiolipins, and anti- β_2 -GPI antibodies and genetic analysis of complement genes was negative. ADAMTS13 activity was within normal ranges (58%). IVIG were withdrawn. Despite daily plasma exchanges from Day 4 to Day 8, the patient developed extensive severe acrocyanosis, anuria, and status epilepticus, prompting us to use salvage therapy by eculizumab (Day 8; 900 mg weekly for 1 month, then followed by 1200 mg every 14 days) after pneumococcal and meningococcal vaccination⁵. Antibiotrophylaxis by ceftriaxone was also started and steroids were maintained. Plasma exchanges were stopped.


As shown in Figure 1C, whereas CK and myoglobin levels were slightly or not modified by steroids, IVIG, and plasma exchanges, the first infusion of eculizumab was followed by a dramatic control of the muscle edema and myalgia. It was also followed by a complete reversal of the distal cyanosis and rapid decline in CK and myoglobin levels. Despite the lack of myositis-specific autoantibodies, RTX was given from days 18 to 40 (375 mg/m² weekly).

Mechanical ventilation and dialysis were withdrawn at days 21 and 28, respectively. Eculizumab was stopped at Month 4 and RTX 500 mg was infused every 6 months. Six months after the admission to the ICU, serum creatinine was 80 μ mol/l, and proteinuria and hematuria were negative. Hypertension was controlled using angiotensin-converting enzyme inhibitor. CK and myoglobin were in normal ranges and the patient did not report muscle weakness. Skin examination was normal. Search for neoplasia was negative.

Data from pathological studies suggest that DM is characterized by an antigen activation of the C5b9 macrophage-activating complex and deposition on the surface of the endothelial cells, with subsequent capillary ischemia and rarefaction, and CD4+ T cells infiltration^{6,7}. Primary and secondary hemolytic and uremic syndromes (HUS), forms of TMA, are also characterized by an uncontrolled activation of the alternative complement pathway. Interestingly, a case of HUS was previously described in a patient with an IIM⁸, reinforcing the potential link between IIM and HUS forms of TMA. In contrast, direct involvement of skeletal muscle is rare in patients with TMA⁹. In this case, we successfully used eculizumab as a salvage therapy for a refractory HUS/TMA¹⁰, with concomitant severe DM. Other immunosuppressive agents helped to control the DM, but the almost complete normalization of the CK level after the first 2 infusions of eculizumab (before the use of RTX), contrasting with the lack of rapid response following steroids and plasma exchange, strongly suggested that

eculizumab was an effective treatment to add-on in severe DM. This finding was similar to that of a previous study that included 10 patients with refractory DM¹¹.

Our case suggests that C5 blocking should be tested in life-threatening or refractory DM.

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