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Case report

RAPIDLY PROGRESSING SYSTEMIC LUPUS ERYTHEMATOSUS IN A YOUNG PATIENT.

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ABSTRACT

Systemic lupus erythematosus (SLE) has a variable clinical expression and can be manifested by a single organ or a multiorgan dysfunction. Patients with this condition have higher associated mortality rates, even when the disease seems clinically stable for many years. An event can occur that deregulates the disease at any given time, making it active or uncontrolled again. In uncontrolled patients, the diagnosis is sometimes difficult and both the approach and treatment are crucial for a favorable outcome. This case report describes the challenging management of a young patient who presented neuropsychiatric manifestations, hematological abnormalities and a rapid development of multiorgan dysfunction. During the patient's hospitalization, three cerebrovascular accidents were registered with a continued worsening of the clinical status, resulting in her death after 33 days. Even with immunosuppression therapy there were several complications, some of which were promptly resolved; however, it was not possible to stop a rapidly progressing autoimmune induced multiorgan failure. The unique features presented by this patient and the rapid progression of the disease are an important alert for all physicians that work in the emergency room.

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1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune pathology with a heterogeneous and variable clinical presentation. The absence of pathognomonic features and unspecific symptoms can lead physicians to a broad spectrum of differential diagnoses, such as hematological, infectious or other autoimmune diseases, making its identification a true challenge (1).

The incidence of the disease has increased over the past years, with regional variations in prevalence and incidence. In Europe, the southern countries seem to have higher rates of SLE, with a wide age range. The incidence is higher in females, especially between the ages of 15-44 years. Generally, it affects non-Caucasian individuals, particularly African-American, which also seem to have more comorbidities and complications associated to this disease (2).

2. Case report

A 25-year-old female, originally from São Tomé e Principe, with a previously known medical history of an ischemic stroke six years prior, resulting in mild dysarthria and left hemiparesis. The stroke etiology was attributed to the presence of an Antiphospholipid Syndrome; therefore, the patient was placed under warfarin anticoagulation therapy. Since then, the patient did not receive any follow-ups. A few years later, we found the diagnosis of a macrocytic anemia and light thrombocytopenia on her medical record (by this time, the patient had abandoned the previous medication). She was advised to restart warfarin and was prescribed vitamin B12 and folic acid supplementation, which she did not comply with.

The patient was admitted to the Emergency Room with complaints of an intense headache with 3 days of evolution, accompanied by diplopia and gradually diminished visual acuity. Concomitantly, she presented dysarthria and a left motor strength of 3/5 (on the scale of muscle weakness) in both limbs, which were sequelae from her prior stroke.

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She presented an ulcerated lesion of 5-6 centimeters in length on her left leg (Figure 1), with a 6-month evolution, according to the patient. She had no other clinical signs or symptoms. The laboratory work-up revealed hemolytic anemia (Hb 5,1 g/dL), low LDH (43 U/L), haptoglobin (8 g/dL), unconjugated hyperbilirubinemia (total bilirubin 1,6 mg/dL; direct bilirubin 0,6 mg/dL), thrombocytopenia ($30x10e^9$/L), hyponatremia (Na 133 mmol/L), normal levels of vitamin B12 and folic acid, hypocomplementemia (C3 67mg/dL, C4 8mg/dL), positive ANA 1.5, anti-DNA 554.7 and positive for antiphospholipid antibody. Cranial CT excluded an acute process.

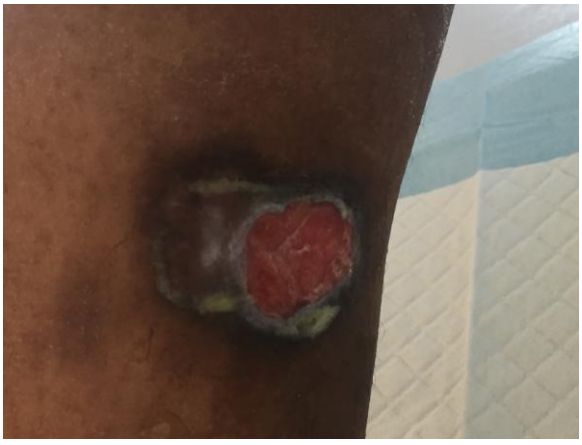

Figure 1. Left leg ulceration 5 to 6 centimeters, with 6 months of evolution but in recovery.

The patient was transferred to the Internal Medicine Department to conduct further investigations and treatment. The patient met 6 criteria for SLE of the Systemic Lupus International Collaborating Clinics (SLICC) classification (positive ANA, anti-DNA and antiphospholipid antibody, hypocomplementemia, hemolytic anemia, thrombocytopenia). One unit of red blood cells was administrated with a good response and high doses of corticotherapy was started.

On the first day, the patient complained of a total lack of visual acuity. The ophthalmologic evaluation found cotton wool spots and bleeding compatible with ocular ischemic syndrome, but due to the low platelet count, no anticoagulation therapy was introduced. The following day, the patient presented diminished muscular strength in all limbs, visual hallucinations and became obtunded. Emergent Cranial CT revealed a focal bleeding brain lesion. After additional studies, the diagnosis of acute transverse myelitis was assumed, with light cord swelling seen on the MRI, accompanied by a neuropsychiatric involvement. Immunosuppression treatment was initiated with azathioprine, mycophenolate acid and rituximab combined with corticosteroids. Anticoagulation therapy was postponed until the 22nd day of hospitalization because of bleeding lesion and low platelet count.

On the 5th day, the patient developed fever, higher inflammatory parameters, acute renal injury and a decreased level of consciousness. This was interpreted as an urosepsis with a multiresistant *Staphylococcus aureus* isolated in urine culture, prompting 7 days of vancomycin therapy. Even with potent immunosuppression therapy and a short-term rehabilitation program, there was no recognized clinical improvement, the patient remained with decreased sensibility in the lower limbs and with a muscle strength of 1/5 in the upper limbs and 2/5 in the lower limbs.

The following days were complicated with another urinary infection and therapy with piperacillin/tazobactam was extended for 14 days, since during the first seven days the patient had recurrent episodes of fever. At the 32nd day, the patient was found in a coma and with metabolic acidosis. Cranial CT scan revealed an acute ischemic stroke associated to cerebral edema with mass effect. Although she was under a therapeutic dose of anticoagulants, it wasn't enough to avoid another ischemic cerebrovascular incident and the patient died one day later.

3. Discussion

The exact pathophysiological mechanism of lupus is not well known; however, it is believed that a multifactorial and complicated relation between various factors can influence the disease's expression. Genetic markers related to major histocompatibility complex, complement and other components of the immune response system can interfere in the process. Deficient immune regulatory mechanism associated to immune tolerance, encourage the formation of pathogenic autoantibodies. The hypothalamo-pituitary-adrenal axis, sex and estrogen levels can also interfere with SLE clinical expression (3). Our patient was a female of African descent in childbearing age with the previous diagnosis of antiphospholipid syndrome (criteria for a higher prevalence) and with positive autoantibodies on admission.

In 2012, SLICC suggested the following classification: (i) acute cutaneous lupus, (ii) chronic cutaneous lupus, (iii) oral ulcers, (iv) nonscarring alopecia, (v) synovitis, (vi) serositis, (vii) renal involvement, (viii) neurological manifestation, (ix) hemolytic anemia, (x) leukopenia or lymphopenia, and (xi) thrombocytopenia as clinical criteria; for other hand, (i) positive ANA, (ii) positive anti-dsDNA antibody, (iii) positive anti-Sm antibody, (iv) positive Antiphospholipid antibody, (v) low complement and (vi) direct Coombs test as immunologic criteria. Four criteria must be present to establish a diagnosis, with at least one being a clinical criteria and one an immunological one (4, 5). The patient presented 7 criteria for the diagnosis of SLE, including the neurological involvement.

Neuropsychiatric involvement has a variable prevalence (14-80%) and a wide spectrum of manifestations, such as seizure, psychosis and neurocognitive dysfunctions. Multiple mechanisms can be involved, such as antibodies, vasculitis, thrombosis, hemorrhages and immunomodulate response. Regardless the dramatic manifestations, there isn't an effective diagnosis technique or treatment (6). The presence of positive antiphospholipid antibodies can be associated with a cognitive dysfunction. Other factors, such as disease activity and chronic damages can contribute to the symptoms' severity (7, 8).

The patient presented a clinically evident neuropsychiatric involvement in less than 12 hours. Immediate immunosuppressing therapy was started to stop the neurological progression and hallucinations ceased after two days. However, the hemorrhagic stroke and the acute transverse myelitis left sequelae that could not be reverted.

Thrombosis in SLE patients are a potential complication that contributes to higher morbidity and mortality rates. The presence of antiphospholipid antibodies predisposes to thrombosis. In SLE, antiphospholipid antibodies are present between 40-60% conferring a higher risk of thrombosis, and other factors such as age, smoking, immunomodulating medication, genetic mutation can contribute to a hypercoagulability state. The anticoagulation therapy is recommended as a preventive measure (9);

however, in some cases the introduction of anticoagulation should be adjusted to the case. This patient had a formal indication, but at the first medical contact she also had low platelet count, representing a high hemorrhagic risk, and anticoagulation therapy exponentially increases the risk of bleeding. Therefore, anticoagulation was not immediately introduced. Even without anticoagulation therapy the patient presented a hemorrhagic event, and after 10 days of starting anticoagulation therapy she suffered an ischemic stroke.

Autoantibody production is frequent in SLE, being directly related to pathological features. Antinuclear antibodies are correlated to activity of the disease and tissue injury, and the anti-dsDNA antibodies are associated with the pathogenesis of immune-complex glomerulonephritis. On the other hand, the autoantibodies are directly responsible for the disease, and can be used as an early marker of SLE, since they can be found before clinical manifestations (9, 10). 6 years prior, the patient had positive antiphospholipid antibodies that increased levels until the last admission, and negative ANA and anti-DNA antibodies became positive. Besides the low levels of complement that were found, translating a severe immunological depression, could explain some of the clinical features described in the presented case.

Corticosteroids and immunosuppressive therapy are recommended when there is neuropsychiatric involvement in SLE. Still, no specific drug is particularly indicated, the type of patient and symptoms' severity determine the drug, or combination of drugs, used. Additionally, the precise moment to introduce immunosuppression therapy, or a combination, is not clear (11), and it takes weeks to reach proper immunomodulation.

In the case discussed, the patient started a high dose of corticotherapy, but unfortunately some hours later, she suffered an ischemic event.

After recognizing a neurological involvement, the immunosuppression with azathioprine, mycophenolate acid and rituximab was initiated, but the clinical status could not be reverted. The prognosis was poor, due to all comorbidities and sustained damaged by diverse mechanisms.

This case illustrates a complex clinical response to a rapidly progressing SLE. SLE can be associated with multiple comorbidities, being aware and recognizing the entity can be of great importance. There is no doubt that an early detection of this condition is critical, especially when there is a neurological involvement, since an adequate treatment may reverse or at least stop the disease progression. SLE has a treatment and, in many cases, it has a favorable outcome.

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