Fever and rash as initial signs of systemic autoimmune disease. Case Report

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Abstract

Introduction: Systemic lupus erythematosus is an autoimmune disorder with a very wide spectrum of clinical presentations. It can affect multiple organs and systems however the disease mainly affects the skin with a variable presentation that can range from the classic butterfly-wing malar erythema to extensive lesions. It affects areas of the face such as the chin and forehead, the trunk, and the extremities. Patients can also present arthralgias, fever of unknown origin, and weight and hair loss. The cause of the fever and the presentation of a rash in the extremities are non-specific symptoms and they represent a challenge for the clinician when trying to find their origin, especially when presented separately, as it was in this case. The diagnosis of the cutaneous manifestations of systemic lupus erythematosus is based on the symptoms, histopathology, and immunohistology of the skin lesions. For the diagnosis of Systemic lupus erythematosus, the 2019 EULAR/ACR classification system is used, which indicates that a total score of ≥10 is required to classify systemic lupus erythematosus. For assessing the activity of Systemic lupus erythematosus, the SLEDAI scale is applied, which indicates that a score of less than 3 is compatible with (low activity), a score of 3-12 (moderate activity), and a score greater than 12 (severe activity).
Objective: To describe one of the diagnostic challenges for the clinician regarding the presentation of fever and rush in SLE or infection since both symptoms can manifest similarly in the two conditions. Therefore, the search for characteristics that allow us to differentiate SLE from infection is a need that must be addressed promptly.
Case presentation: The following case describes a 15-year-old female who presented with fever and skin rash separately for 1 month, as the initial manifestation of SLE. Additionally, the patient responded adequately to immunosuppressive treatment.
Conclusions and recommendations: Systemic lupus erythematosus underlies a wide spectrum of clinical presentations with repercussions at the level of organs and systems that can present with symptoms. In this case, fever and rash appeared separately within 1 month of evolution. Other symptoms such as weight loss, asthenia, and hair loss occurred upon admission of the patient. The diagnosis should be based on the exclusion of other pathologies, timely examinations, and adequate immunosuppressive treatment, as well as distinguishing whether the fever is due to an active infectious process or is secondary to the activity of systemic lupus erythematosus.

Keywords: Lupus Erythematosus, Systemic, Fever, Exanthema, Autoimmune Diseases, Lupus Erythematosus, Cutaneous.

Fiebre y rash como signos iniciales de una enfermedad autoinmune sistémica. Reporte de caso

Resumen:

Introducción: El lupus eritematoso sistémico es un trastorno autoinmune con un espectro muy amplio de presentaciones clínicas. Puede afectar múltiples órganos y sistemas, sin embargo, la enfermedad afecta principalmente a la piel con una presentación variable que puede ir desde el clásico eritema malar en alas de mariposa hasta lesiones extensas. Afecta zonas del rostro como el mentón y la frente, el tronco y las extremidades. Los pacientes también pueden presentar artralgias, fiebre de origen desconocido y pérdida de peso y cabello. La causa de la fiebre y la presentación de un sarpullido en las extremidades son síntomas inespecíficos y representan un desafío para el clínico al intentar encontrar su origen, especialmente cuando se presentan por separado, como fue en este caso. El diagnóstico de las manifestaciones cutáneas del lupus eritematoso sistémico se basa en los síntomas, la histopatología y la inmunohistología de las lesiones cutáneas. Para el diagnóstico del lupus eritematoso sistémico se utiliza el sistema de clasificación EULAR/ACR de 2019, que indica que se requiere una puntuación total ≥10 para clasificar el lupus eritematoso sistémico. Para evaluar la actividad del lupus eritematoso sistémico se aplica la escala SLEDAI, que indica que una puntuación inferior a 3 es compatible con (actividad baja), una puntuación de 3 a 12 (actividad moderada) y una puntuación superior a 12 (actividad severa).
Objetivo: Describir uno de los desafíos diagnósticos para el clínico respecto a la presentación de fiebre y exacerbación en el LES o infección ya que ambos síntomas pueden manifestarse de manera similar en las dos condiciones. Por tanto, la búsqueda de carac-

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terísticas que nos permitan diferenciar el LES de la infección es una necesidad que debe abordarse con prontitud.
Presentación del caso: El siguiente caso describe una mujer de 15 años que presentó fiebre y erupción cutánea por separado durante 1 mes, como manifestación inicial de LES. Además, el paciente respondió adecuadamente al tratamiento inmunosupresor.
Conclusiones: El lupus eritematoso sistémico subyace a un amplio espectro de presentaciones clínicas con repercusiones a nivel de órganos y sistemas que pueden presentar síntomas. En este caso, la fiebre y el sarpullido aparecieron por separado al mes de evolución. Otros síntomas como pérdida de peso, astenia y caída del cabello se presentaron al ingreso del paciente. El diagnóstico debe basarse en la exclusión de otras patologías, exámenes oportunos y un tratamiento inmunosupresor adecuado, así como distinguir si la fiebre se debe a un proceso infeccioso activo o es secundaria a la actividad del lupus eritematoso sistémico.

Palabras clave: lupus eritematoso sistémico, fiebre, exantema, enfermedades autoinmunes, lupus eritematoso cutáneo.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous characteristics, which is usually distinguished by the presence of many different autoantibodies and inflammation present in multiple organs. Its clinical presentation can range from a mild disease involving the skin and joints to a life-threatening condition with systemic involvement. Patients with SLE experience a considerably reduced quality of life compared to the rest of the population[1]. It is recognized that although this disease can occur in both sexes, it has a higher incidence in young and middle-aged women, mainly around 30 years of age. The skin is one of the target organs most variably affected by the disease for this reason the European Alliance of Rheumatology Associations (EULAR) and the American College of Rheumatology (ACR) in 2019 modified the criteria for the diagnosis of SLE. Its classification requires the presence of positive antinuclear antibodies (ANA) as primary criteria and additional criteria[2]. The clinical picture of SLE is variable as it can range from mild involvement of the joints and skin to a potentially life-threatening systemic involvement.[3] On the other hand, cutaneous lupus erythematosus (CLE) is an exclusive skin disease that is 2 to 3 times more common than SLE, and this is because not all people with CLE meet all the criteria EULAR/ACR (2019) for the diagnosis[4-14] of SLE. The clinical spectrum of CLE includes three categories of specific skin diseases from the nosography concept:

1-Acute cutaneous lupus erythematosus (ACLE): This type can be present in 90% of patients diagnosed with SLE and its symptoms appear over months or years. The affected skin feels warm and appears slightly edematous. The presence of an erythematous (morbilliform) maculopapular rash is also common, which reappears especially with sun exposure[4-14].

2-Subacute cutaneous lupus erythematosus (SCLE): This type is associated in 50% of cases with SLE, approximately 10 to 15% of patients who present with SCLE develop severe clinical manifestations of SLE, central nervous system, or kidney disease. The lesions are usually erythematous with variable amounts of scaly wounds. The most common sites of involvement include the shoulders, forearms, neck, and upper torso[4-14].

3-Chronic cutaneous lupus erythematosus (CCLE): This type has a very varied presentation, which is why it has been divided into: discoid lupus erythematosus (DLE), lupus erythematosus tumidus (LE tumidus), deep lupus (lupus panniculitis), chilblains lupus erythematosus (chilblains LE tumidus), and finally the lichenoid cutaneous lupus erythematosus-lichen planus overlaps syndrome (LE-LP overlap syndrome) [4-14].

Finally, fever, anorexia and skin rash are common manifestations of SLE whose clinical picture can be present at the beginning of the disease, but they don't differentiate the diagnosis of SLE from other systemic diseases or infectious processes. Persistent high fever above 38.6°C may even occur. However, in these cases the possibility of the existence of a coexisting infection must always be eliminated considering the prolonged evolution time, lack of clinical findings and laboratory tests that don't confirm a present infection, which in the end represents a challenge diagnosis [5].

Case presentation

A 15-year-old woman with clinical symptoms of 2 months of evolution characterized by fever up to

39°C which appeared recurrently with an average duration of 5 days and whose only accompanying symptom was the presence of skin rashes that were intermittent with unknown origin. The patient was first treated with antibiotics and topical corticosteroids, which were prescribed by different doctors and without finding improvement. She also reported the presence of recurrent abdominal pain for 2 days that improved with analgesics and didn't reappear until she was subsequently admitted to the hospital.The patient indicated that she had received several treatments without improvement.

A few days later the patient was evaluated by our emergency service and upon admission the only symptoms the patient presented were fever and erythematous lesions with a tendency to Scar. It was decided to admit her to the internal medicine service for investigation. She was monitored 24 hours after admission to the emergency room, finding the presence of weight loss of approximately 10 kg and the presence of non-pruritic erythematous lesions on the skin of the arms and anterior chest in the last 3 months, accompanied by abdominal pain, cough, vomiting, asthenia, appetite loss and hair loss, lasting 48 hours.

The physical exam revealed blood pressure (BP) of 100/60 mmHg, heart rate (HR) of 100 beats per minute (BPM), respiration rate (RR) of 20 respirations per minute (RPM), oxygen saturation of 93% room air, Temperature of 38.6°C (which didn't improve with antipyretics), weight of 50 kilograms, height of 152 centimeters. The skin presented scarring alopecia with greasy hair that falls easily. In addition to asymmetrical erythematous-type skin lesions with a tendency to be scaly-like and purplish color present at the level of the neck, anterior thorax, elbow, armpits, and lower limbs (Figure 1). The abdomen was soft, depressible, and the patient experienced pain during deep palpations in the epigastrium and colonic framework. Lower extremities didn't present edema, however there was difficulty in movement which was associated with skin lesions. The patient didn't present respiratory symptoms. There were also no signs of neurological focalization and no signs indicating an active infection.

On the first day upon admission, the first laboratory tests report leukopenia (4.3x 103/mm^3) and hypochromic normocytic anemia (hemoglobin 7.3 g/dL), negative urine test for protein, blood, and infection. Subsequently, the patient was stabilized, based on the clinic. Since the cause of origin for the patient symptoms wasn't found, an autoimmune disease was suspected. Autoantibodies tests were requested, finding the presence of positive antinuclear antibodies (ANA) of 1:1280 fine granular nuclear pattern, positive serology for double-stranded Anti-DNA with 1354.64 IU/mL, positive Anti RO (SS-A) antibodies with result of > 200.0 U/mL, Anti-RNP/Sm Antibodies positive with 92.60 U/mL, Anticardiolipin IgM Antibodies positive with 9.90 MPL-U/mL, Sm Antibodies positive with 93 0.50 U/ml.

With these results, the patient started specific targeted treatment. After the patient was seen by the dermatology service, which requested a skin biopsy that reported the presence of interface dermatitis with vacuolar degeneration of the basal layer, incontinence pigmentosa, perivascular and interstitial infiltrate, predominantly lymphocytic, compatible with SCLE (Figure 3). Based on the abdominal pain that shows no improvement and the high morbidity of patients who present subacute cutaneous lupus erythematosus a simple abdominal CT scan was performed. The scan revealed free fluid in the parietal-colic grooves and at subphrenic level. There were also thicken loops at the jejunum, ruling out signs of mesenteric ischemia which is why it was classified as inflammatory ascites. With the aforementioned, the EULAR/ACR classification system is applied, obtaining a score of 25 points (fever, alopecia, subacute cutaneous lupus, leukopenia, anticardiolipin positive, double-stranded anti-DNA positive, anti-SM positive) compatible with a diagnosis of SLE.

The SLEDAI scale was also applied to evaluate the activity index of the disease, obtaining a score of 6 points (alopecia, fever, leukopenia, inflammatory rash) compatible with a moderate activity of the disease. Despite the antipyretic treatment that the patient received, she persisted with febrile episodes without an apparent infectious origin. Next the treatment consisted of antimalarials, oral corticosteroids, anticoagulation with low-dose enoxaparin and azathioprine, as indicated by the European Alliance of Rheumatology Associations (EULAR 2019), which resolved the febrile episode and indicated that the thermal rises were due to the activity of the SLE (outbreak of lupus).

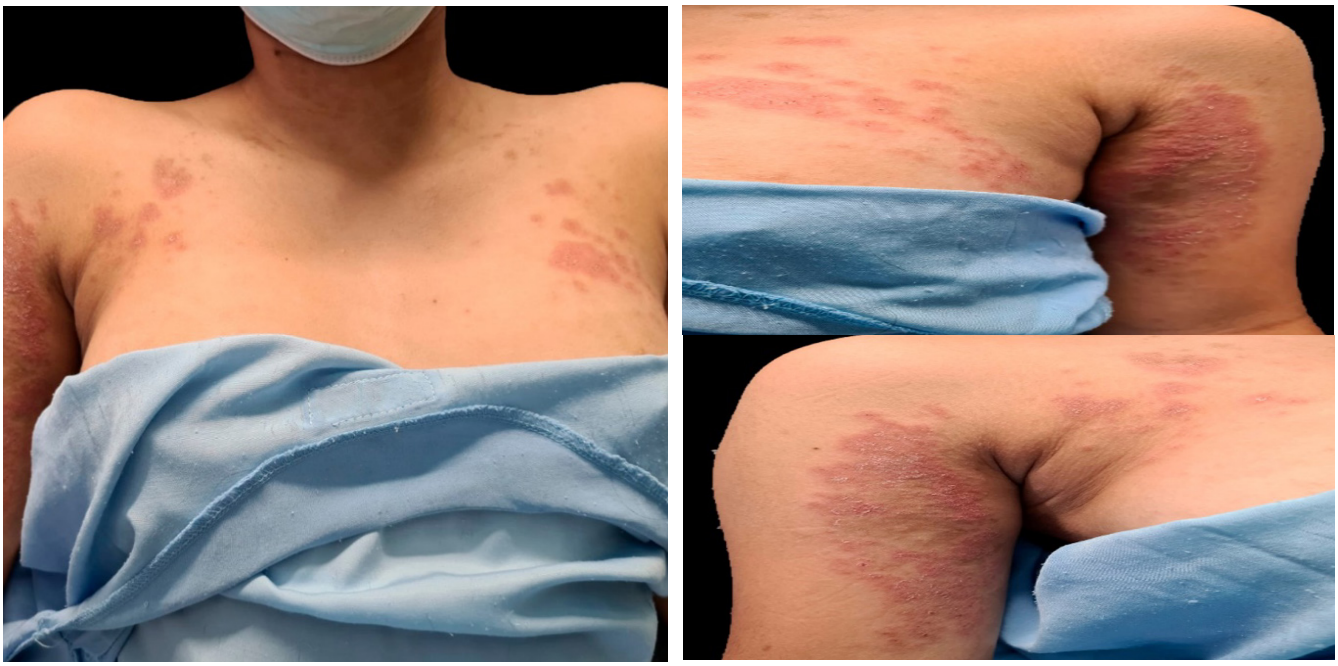

Figure 1: Asymmetric skin lesions characterized by erythematous plaques with a tendency to be scaly with a purplish color and slight central scarring.

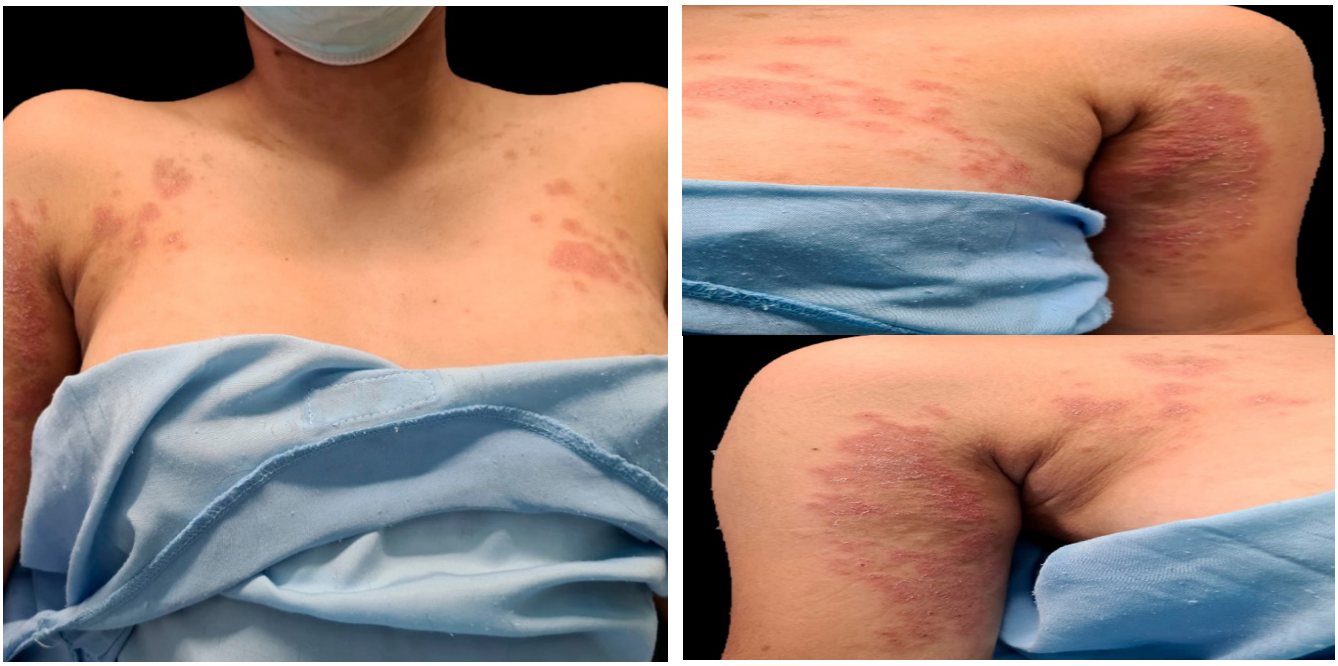

Figure 2: Images of skin lesions after treatment.

After what was mentioned regarding the clinical evolution of the patient, it was observed that with the treatment the skin lesions improved. There was no presence of abdominal pain, absence of fever or vomiting and without any other symptoms (Figure 2). Therefore, medical discharge was decided with treatment based on hydroxychloroquine, prednisone, and azathioprine.

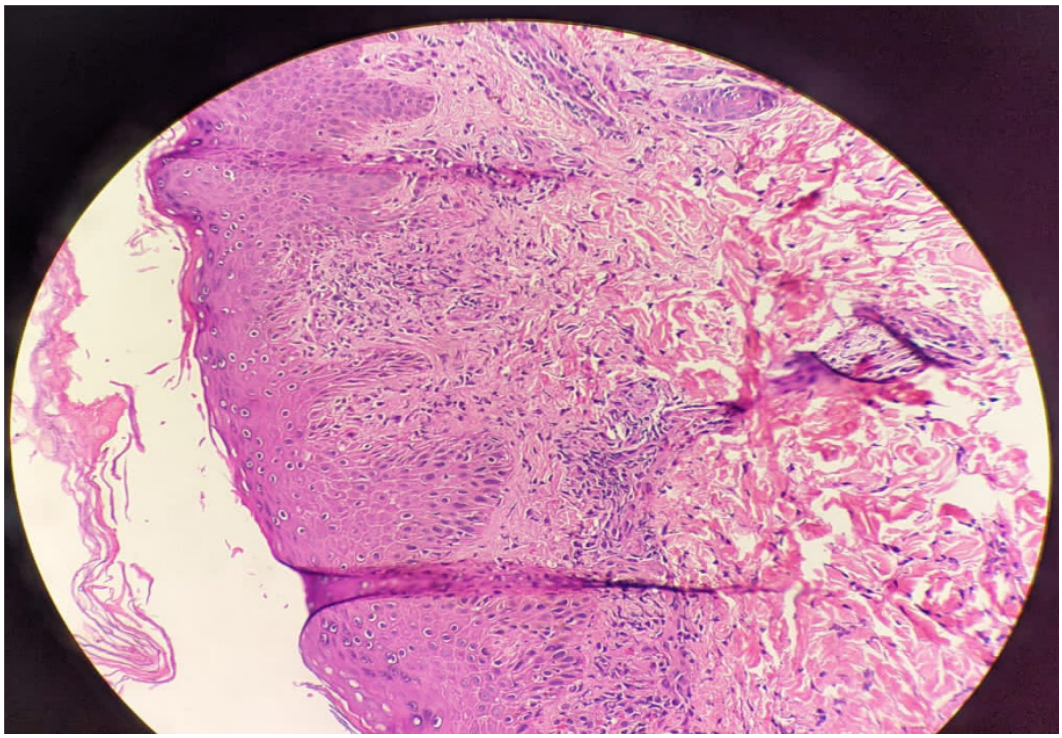

Figure 3: Interface dermatitis with vacuolar degeneration of the basal layer, incontinence pigmentosa, perivascular and interstitial infiltrate, predominantly lymphocytic, consistent with subacute cutaneous lupus erythematosus.

Discussion

The heterogeneity of the clinical presentation of this disease represents a challenge for medical diagnosis[3]. Within the clinical presentation of SLE there are signs and symptoms by systems, presenting at hematological level in 55 to 77% anemia, lymphopenia, leukopenia, and thrombocytopenia. At the mucocutaneous level in a 70% malar rash, photosensitivity, oral or nasal ulcers, and discoid rash. At the musculoskeletal level 61 to 64% arthritis, arthralgia and serositis. At the renal level in a 27 to 59% proteinuria, hematuria, cylinders suggestive of nephritis, nephrotic syndrome, and biopsy-proven lupus nephritis[15,16]. Finally, we have a fever in a 26 to 58%, and other characteristic signs such as Raynaud's phenomenon, pleurisy, and dry symptoms (dry eyes, dry mouth)[4]. The pathogenesis of the disease is still unclear, but it is considered that it can be caused by immune pathways leading to the presence of pathogenic autoantibodies, some of which react with antigens to form immune complexes (IC), consisting of nucleic acids and perhaps other nuclear (and even cytoplasmic) compounds[5]. The origin of skin lesions in SLE is linked to exposure to ultraviolet light that activates keratinocytes that resulting in their apoptosis. The other lesions are produced through the formation of immune complexes and complement activation that generates a local inflammatory response[6].

The diagnosis of SLE depends on the form of presentation and the exclusion of alternative diagnoses. Common laboratory findings in patients with SLE include the presence of autoantibodies such as ANA, antibodies against double-stranded DNA (dsDNA), antibodies against extractable nuclear antigens (ENA), and antiphospholipid. It is important to recognize that if ANA is positive, other specific antibodies should be tested, such as anti-dsDNA, anti-Smith (anti-Sm), Ro/SSA, La/SSB, and U1 ribonucleoprotein (RNP)[3], especially to establish its association with other pathologies such as Sjögren's syndrome or connective tissue disease[4]. In patients with SLE and skin lesions, taking a biopsy with histopathological examination can lead to a diagnosis compatible with CLE, presenting characteristics such as vacuolar interface dermatitis, hyperkeratosis, epidermal atrophy, a superficial, perivascular, and inflammatory infiltrate, mononuclear cell perifollicular; thickening of the basement membrane; and incontinence pigmentosa[8].

With respect to fever, it is known that there are many mechanisms by which it occurs, one of them being the conformation and alteration of the inflammasome with the subsequent release of interleukins. It is know that the cause of fever in patients diagnosed with SLE can be an underlying infection. After ruling out infection, fever associated with SLE activity should respond to NSAIDs, acetaminophen and/or low to moderate doses of glucocorticoids. If the fever doesn't subside after such treatment the suspicion of an infectious etiology is further raises[6]. In previous investigations, it has been indicated that elevated C reactive protein (CRP) levels (above 6mg/dl) are highly suggestive of infection and may together with other laboratory findings could help diagnose a present infection, as well as typical signs of SLE activity, such as decreased complement or increased activity of SLE, measured by the SLEDAI index, the use of the neutrophil/lymphocyte index has also been emphasized, since it has been seen that a value ≥3 correlates with active inflammation, both in the lupus flare as in other inflammatory diseases, infections, and cancer. On the other hand, the use of high doses of steroids in lupus patients with infection has led to fatal sepsis, hence the importance of differentiating both situations well.[12, 13, 17]

The treatment of systemic lupus erythematosus depends on the severity and manifestations of the disease. In a study called LUMINA (Lupus in Minorities: Nature versus Nurture), have offered evidence of a decrease in flare-ups and prolonged life in patients receiving hydroxychloroquine, which makes it the cornerstone of SLE treatment according to the European Alliance of Rheumatology Associations in 2019.[18]. It also mentions that cases of mild disease are often controlled with non-steroidal anti-inflammatory drugs (NSAIDs) or low potency immunosuppressive drugs, such as short courses of corticosteroids. On the other hand, the use of steroids in a prolonged manner is reserved for patients with compromise of vital organs. Steroid administration can be intravenous or orally depending on the clinical status or systemic involvement, with preference for the intravenous route in the event of a severe lupus flare. The use of immunosuppressants such as methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide is also mentioned in cases of patients with persistent symptoms despite the use of steroids[9, 10].

Conclusion

Early-onset systemic lupus erythematosus is a rare pathology that is often underdiagnosed when a comprehensive approach to the patient is not performed. The differentiation between symptoms due to an infectious disease and one due to an autoimmune process must be understood and analyzed. Therefore, its diagnosis, differentiation, and management must be optimal, and it should be based on existing recommendations. Before initiating immunomodulatory treatment, it is necessary to rule out any infectious origin that the fever may have, as administering corticosteroids to patients with active infections could potentially lead to septicemia. Finally, it is necessary to promote a teaching campaign for the recognition of autoimmune diseases so that those who need care are referred correctly and don't wait for them to become complicated cases.

Abbreviations

SLE:	Systemic lupus erythematosus
EULAR:	European Alliance of Rheumatology Associations
ACR:	American College of Rheumatology
ANA:	Antinuclear antibodies
CLE:	Cutaneous Lupus Erythematosus
ACLE:	Acute cutaneous lupus erythematosus
SCLE:	Subacute cutaneous lupus erythematosus
CCLE:	Chronic cutaneous lupus erythematosus
ENA:	Extractable nuclear antigens

Approval and informed consent

Written informed consent was obtained from the patient for publication of this case report; No patient identifying information was used in the publication of this article.

Authors' contributions

All authors contributed to the concept and design of the study, performed acquisition of data, analysis, and interpretation, drafted the manuscript, critically revised the manuscript for important intellectual content, and read and approved the manuscript.

Conflict of interests

The authors declare that they have no conflicting interests.

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