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Case Report

Systemic Lupus Erythematosus Associated With Chronic Cocaine Use☆

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ABSTRACT

Systemic lupus erythematosus is an autoimmune disease of unknown aetiology that manifests as a pleomorphic systemic disease that mainly affects women. The autoimmune mechanism of systemic lupus erythematosus has been associated with the development attributed to the development of phagocytosis, produced by the neutrophils (of the nuclei released by cells that are opsonised by anti-DNP antibodies and C3b. A multifactorial aetiological relationship has been observed in various studies and the induction of autoimmune diseases, such as the uncommon relationship with the chronic abuse of cocaine. This can be explained through biological processes, where phagocytosis of the rests of cells generated by these diseases is inhibited.

The case is presented of a male patient with history of consumption of benzoylecgonine derivatives and presented with constitutional, lung, kidney, skin and musculoskeletal manifestations. The laboratory results and renal biopsy confirmed the diagnosis of systemic lupus erythematosus with nephritis lupus class IV. Emphasis is placed on the importance of the suspicion and early diagnosis of the disease, and correlation with the consumption of cocaine in order to give early treatment, as well as preventing its progression and complications.

Lupus eritematoso sistémico asociado al consumo crónico de cocaína

Palabras clave:
Lupus eritematoso sistémico
Vasculitis

RESUMEN

El lupus eritematoso sistémico (LES) es una enfermedad autoinmune, de etiología desconocida, que se manifiesta como una enfermedad sistémica pleomórfica, afectando, principalmente, a las mujeres. El mecanismo autoinmune del LES se ha visto asociado

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al desarrollo del fenómeno de la célula LE. Este fenómeno consiste en la fagocitosis, por parte de los neutrófiflos, de los núcleos liberados por las células opsonizadas por el anticuerpo anti-DNP y el complemento C3b. A partir de diferentes estudios, se ha visto relación multifactorial etiológica en la inducción de enfermedades autoinmunes, en la que se encuentra una relación infrecuente con el consumo crónico de cocaína. Esto se explica a través de procesos biológicos en los que se inhibe la fagocitosis de los restos celulares generados por dichas enfermedades. A continuación se presenta el caso de un paciente con antecedente de consumo de derivados de la benzoilecgonina, quien ingresa por manifestaciones constitucionales, pulmonares, renales, cutáneas y musculoesqueléticas, en quien los paraclínicos y la biopsia renal confirman el diagnóstico de LES con nefritis lúpica clase iv. Así mismo, se destaca la relevancia de sospecha y diagnóstico temprano de dicha enfermedad y la correlación con el consumo de cocaína para dar tratamiento oportuno y evitar el progreso y sus complicaciones.

Introduction

Systemic lupus erythematous (SLE) is a disease that affects millions of people worldwide. For its diagnosis are used the SLICC criteria, established in 2012 by the Systemic Lupus Collaborating Clinics, that give more importance to the autoimmune profile, in addition to having the characteristic of being cumulative, which allows a greater inclusion, and therefore, increases the sensitivity.[1] It is of utmost importance to detect the disease timely, since the survival of patients with SLE is favorable, being of 95% 5 years after diagnosis, and of 92% within 10 years; however, the progression of the disease to lupus nephritis reduces survival to 88% in 10 years.[2]

The autoimmune component is originated by defects in the deletion of autorreactive B and T lymphocytes, along with the presence of autoantigens in the surface of the cell membranes, which generate an abnormal immune response against the own body, causing direct damage to the cells. Cocaine affects in a higher proportion the ability of the phagocytic cells to eliminate bacteria and tumor cells, among other cell debris, probably by the suppression of their ability to generate effector molecules such as nitric acid, the alteration of the acidification, in addition to the inhibition of the aggregation and adhesion of the neutrophils to the vascular endothelium, which limits the phagocytosis. Cocaine use has to be repetitive to observe its complete suppressive effects.[3]

We present the case of a patient with SLE associated with chronic cocaine use, which predominates in males, without establishing the incidence or the prognosis due to its low frequency. This is the first case published in Latin America and the second in literature.

Clinical Case

It is about a 34-year old male patient, who arrived with a picture of 15 days of evolution, consisting in progressive dyspnea classified 3/4 in the modified Medical Research Council scale, associated with dry cough and chest pain of bilateral pleuritic characteristics, of 7/10 intensity, accompanied by facial edema, asthenia and adynamia. In addition, he referred occasional gross hematuria with foamy urine. In the systems review, he referred arthralgia of all the metacarpophalangeal joints without edema. As an antecedent of importance he described frequent cocaine use for 18 years (3 pipes per day), being his last consumption 15 days before the consultation. Upon his arrival to the institution high pressure values (systolic blood pressure readings between 140 and 160) were documented, and as a positive finding on the physical examination, the presence of a lesion on the face, indicative of malar erythema (Fig. 1), lung auscultation with bi-basal wheezing, crepitant rales and edema in the face and the lower limbs. Synovitis, stiffness, deformity or enthesitis were not documented.

Paraclinical tests were performed, which reported lymphopenia, thrombocytopenia, hypoalbuminemia, hypercholesterolemia, and increase of nitrogen compounds. In addition, urinalysis with proteinuria, upper and lower tract hematuria, pyuria and sediment with presence of hematic and granular cylinders. Proteins in 24-hour urine: 11.42 g. The imaging study of the kidneys and the urinary tract describes enlarged kid-

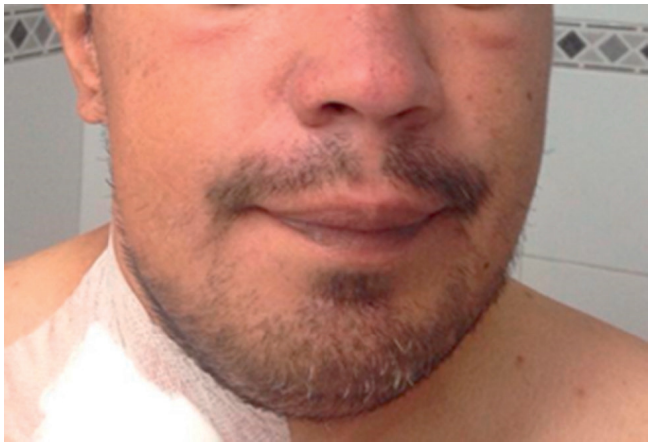

Figure 1 – Erythematous-violaceous plaque located in the bilateral malar region with extension to the dorsal region of the nose, respecting the nasolabial folds.

Table 1 – Autoimmunity Study in the Patient.

Autoimmunity	Results
Anti-DNA	> 1:40
Antinuclear	> 1:320
Complement C3	33.3
Complement C4	< 5
Extracted from the nucleus	–
IgM cardiolipin	21.49
IgG cardiolipin	36.82
IgM antiphospholipids	18.86
IgG antiphospholipids	16.19
Antineutrophil cytoplasmic	1:20
Cytoplasmic pattern	–
Perinuclear pattern	> 1:80
Myeloperoxidase	3.91
Antiproteinase 3	4.23
Anti-cyclic citrullinated peptide	5.58
Hepatitis B surface antigen	–
Hepatitis C antibody	–
IgM anti-core antibody	–

neys, without alteration of the corticomedullary relationship. In the presence of high blood pressure, upper tract hematuria and commitment of the renal function with preserved morphology, the presence of rapidly progressive glomerulonephritis was considered. The exams were complemented with autoimmunity studies (Table 1). Additionally, it was requested a chest X-ray, which showed diffuse interstitial opacities, of predominantly apical reticular pattern, elevation of the right hemidiaphragm with obliteration of the costophrenic angle, indicative of lung disease due to chronic cocaine use; and for this reason it was performed a high resolution computed tomography of the chest, in which predominates the presence of cystic changes with areas of emphysema, findings described in chronic exposure to cocaine. (Fig 2).

Considering all the above, the presence of an immunologic profile positive for antinuclear antibodies, anti-DNA, anticardiolipin and hypocomplementemia, hematologic involvement, cutaneous manifestations and serositis, a diagnosis of a picture compatible with active SLE is made, through the systemic lupus erythematosus disease activity index 21 (SLEDAI 21), with a probable aetiologic relationship with cocaine use, possibly adulterated with levamisole (information on the component provided by the patient). Because of the severe activity, especially the involvement of the renal function, metilprednisolone 1 g/day, for 3 days, was indicated, continuing with prednisolone 1 mg/kg/day and chloroquine 250 mg/day. Due to the rapid deterioration of renal function, we considered pertinent to start the renal replacement therapy and to perform a renal biopsy in order to stage and classify the renal involvement by lupus, with a view to establish the need for induction therapy.

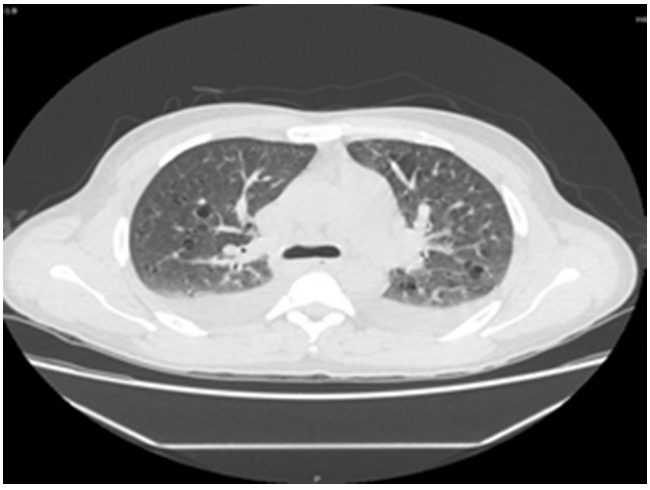

Figure 2 – Chest HRCT. Bilateral pleural effusion, areas of centrolobulillar emphysema and multiple cysts with areas of cystic destruction. The cysts vary in size from 18 to 22 mm. Signs of precapillary pulmonary hypertension.

The renal pathology reported class IV lupus nephritis (Fig. 3). With these results of the biopsy, immunosuppressant management with cyclophosphamide 15 mg/kg was started.

The respiratory manifestations were managed symptomatically with inhaled beta agonist and anticholinergic agents, associated with respiratory therapy, achieving resolution of symptoms, but requiring continuity of management with supplementary oxygen at home.

Discussion

Cocaine is a hallucinogenic drug of the genus *Erythroxylum,* being the second most commonly used hallucinogenic worldwide. Since 2002, levamisole has been used as a cocaine adulterant. Its use has increased over time, until reaching approximately 70% of the cocaine seized by the Drug Enforcement Administration (DEA) in the United States.[4-6]

The adulteration of cocaine with levamisole has increased because it has certain favorable physical-chemical characteristics in terms of the enhancing effects that it produces, as well as of the availability and accessibility that facilitate its sale.[7] Levamisole is an anthelmintic agent which is currently being used in veterinary medicine.[8] Previously, it was used in treatments for rheumatoid arthritis, nephrotic syndrome, and cancer of the colon and the mammary glands.[4,8,9] However, the product had to be withdrawn from the market in 1999 because there were detected adverse reactions such as agranulocytosis, which has been associated with the presence of HLA B27, in several cases, and cutaneous vasculitis.[4,7,8] It has also been reported that levamisole promotes the chemotaxis of neutrophils, the proliferation of T-cells, the maturation of dendritic cells and the induction of the circulation of antibodies in the plasma, which explains its effects of autoimmunity.[10] One of the abnormal adverse effects of levamisole is the vasculitis, which occurs with cutaneous manifestations such as lesions of purpuric reticular pattern, with or without necrosis or phlyctenas, mainly in the helix and the extremities. They can also be evidenced in the trunk and in the malar region; in addition to arthralgia, hemolytic anemia and agranulocytosis. In this way, it unmasks latent immunologic abnormalities, forming antibodies against neutrophil elastase, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and lupus anticoagulant.[7] The problem for the detection

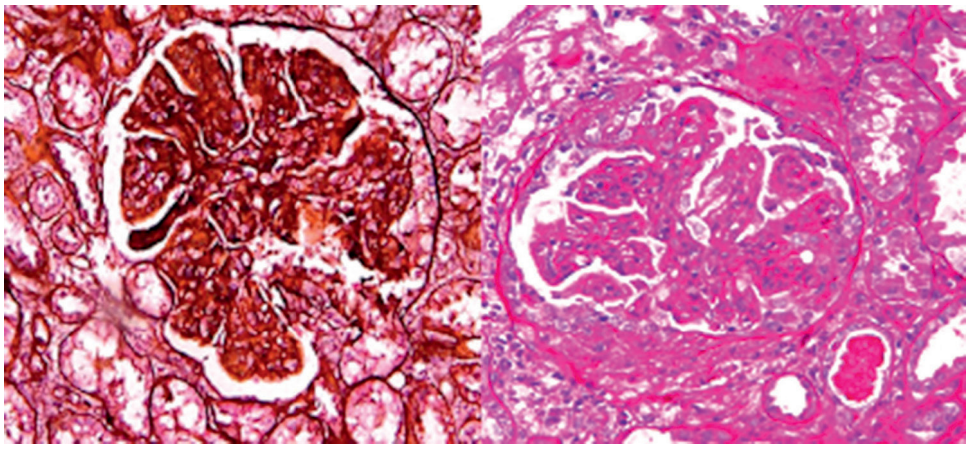

Figure 3 – Renal biopsy with immunofluorescence. Endocapillary cell proliferation, thickening of the basement membrane, hyaline deposits and images of karyorrhexis. In the immunofluorescence study there are 4 glomeruli with: lgG: punctiform in the basement membrane ++ + +, C1q: punctiform in the basement membrane and mesangium +++, C3: punctiform in the basement membrane and mesangium ++, C4: (–), lgM: punctiform in the basement membrane and mesangium ++, lgA: punctiform in the basement membrane and mesangium ++.

of levamisole in the human body lies in the fact that it has a very short half-life (5.5 h) an only 2.5% is excreted in the urine.[4,7,11,12]

The pulmonary complications of cocaine are influenced by the method of administration, the size of the dose and the presence of associated substances (e.g., heroin, talc). These complications include acute respiratory symptoms, barotrauma, asthma, pulmonary edema, hemoptysis and pulmonary hemorrhage, "Crack lung", secondary organizing pneumonia, talcosis, silicosis, interstitial lung disease, pulmonary hypertension, emphysema, infection, aspiration pneumonia and tumors.[13]

Six patients with SLE, who in addition consumed cocaine in a chronic way and none of them had a family history of SLE or any autoimmune disease were described in 2009, being the only publication to date.[14] The importance of such cases is due to the similarity of the manifestations exhibited by these patients with respect to ours and because they are the only ones reported in the literature. Likewise, they have in common with our patient the male gender, chronic cocaine use, age of onset (between 20-45 years), lymphopenia, serositis, presence of antinuclear antibodies and renal involvement. Other findings are also associated between both cases, such as thrombocytopenia and the presence of anti-DNA and antiocardiolipin antibodies. Our report shares the limitations inherent to the case reports with small samples. The manifestations of SLE that were evidenced in our patient are summarized in Table 2.

The autoimmune mechanism of SLE has been associated with the development of the LE cell phenomenon, which is characterized by the formation of polymorphonuclear cells containing nuclear material. In recent years, it has been demonstrated that the antibodies generated in the disease can penetrate into the cells, translocate the nucleus and activate an apoptotic response through the Fas/Fas ligand. Then the remaining apoptotic bodies are phagocytosed by a polymorphonuclear neutrophil, thus forming the LE cell.[15] However, it has been demonstrated that this disease produces abnormalities in the apoptosis pathways and therefore, defects in the deletion of autorreactive cells are generated, thus progressing to autoimmunity and tolerance.[16]

Likewise, at the cellular level the use of cocaine induces apoptosis of epithelial cells, neurons and cardiomyocytes, alters the fluidity of the cell membranes, and decreases the

Table 2 – Manifestations Present in the Patient.

Lupus manifestations	Results
Age at diagnosis	34 years
Ethnicity	mestizo
Malar erythema	+
Photosensitivity	–
Discoid lupus	–
Oral ulcers	–
Serositis	+
Arthritis	–
Renal involvement	+
CNS involvement	–
Leukopenia	–
Lymphopenia	+
Anemia	–
Thrombocytopenia	+
Antibodies	
ANA	+
Anticardiolipin	+
Anti-DNA	+
ANCAS	
c-ANCA	–
p-ANCA	+
Complement C3	Consumed
Complement C4	Consumed
Myeloperoxidase	–
Antiproteinase	–

process of phagocytosis, in addition to generating an alteration in the phagolysosomal acidification, which normally allows the maturation of proenzymes and the release of neutrophil granules.[3] On the other hand, cocaine has effects on two of the main enzymes involved in the process of degranulation of neutrophils, such as beta-glucoronidase and lysozimes, which contain azurophilic granules and specific granules.[17]

In this way, the induction of the cell apoptosis by the antibodies generated by the SLE and the inhibition of the phagocytosis and the acidification of the phagolysosome, due to the cocaine use, bring as consequence the presence of non-phagocytosed apoptotic cell debris, and therefore, their presentation by the dendritic cells and the production of more autoantibodies, thereby stimulating the progression of the disease. Likewise, the production of cytokines and the inflammatory process increase in the disease, producing autorreactivity of the T/B cells.[13]

An increase in the survival rate from 40% to 90% has been evidenced in the middle of the 20th century, from 1950 to 1980, given the early detection, the increase of the sensitivity of the diagnostic tests and the new therapies. However, the prognosis worsens with the presence of complications.[18] Despite the availability of new therapeutic regimens, it has been detected a poor response to them in patients who already have lupus nephritis, which is the most devastating complication of SLE.[2] The response to the treatment and the prognosis of the patients with SLE induced by cocaine are similar to those described in the literature, so it is of utmost importance to consider the interaction that exists between cocaine and SLE in order to remove the noxa, begin the proper treatment and prevent the progression of complications.

Definitively, in our case is evidenced a male patient with SLE that through cellular mechanisms, generates apoptosis of the own cells and secondarily develops autoantibodies. On the other hand, he has a history of chronic cocaine use, which through previously explained biological processes induces and promotes the progression of the disease to devastating stages.

Conclusion

The development of autoimmunity is multifactorial, situation in which the consumption of psychoactive substances, such as cocaine adulterated with levamisole, evidence an induction potential; therefore, being aware of the history of consumption in a patient with these clinical manifestations, without a family history, is very important for the diagnosis. However, although the early initiation of the treatment has impacted the evolution of this type of diseases, the withdrawal of the exposure to psychoactive agents and the severity of the involvement of a target organ (particularly the kidney) have an implication in the morbidity and mortality due to SLE.

Ethical Disclosures

Protection of people and animals. The authors declare that the procedures followed were in accordance to the ethical standards of the responsible committee on human experimentation and according with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Protection of people and animals. The authors declare that the procedures followed were in accordance to the ethical standards of the responsible committee on human experimentation and according with the World Medical Association and the Declaration of Helsinki.

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Petri M, Orbai AM, Alarcón GS, Gordon C, Merril JT, Fortin PR, et al. Derivation and validation of Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythemathous. Arthritis Rheum. 2012;64:2677-86.
2. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American college of rheumathology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64:797-808.
3. Mukunda BN, Callahan JM, Hobbs MS, West BC. Cocaine inhibits human neutrophil phagocytosis and phagolysosomal acidification in vitro. Immunopharmacol Immunotoxicol. 2000;22:373-86.
4. McGrat MM, Isakova T, Rennke HG, Mottola AM, Laliberte KA, Niles JL. Contaminated cocaine and antineutrophil cytoplasmic antibody-associated disease. Clin J Am Soc Nephrol. 2011;6:2799-805.
5. Espinoza LR, Pérez Alamino R. Cocaine-induced vasculitis: clinical and inmmunological spectrum. Curr Rheumatol Rep. 2012;14:532-8.
6. John S, Manda S, Hamrock D. Cocaine-induced thrombotic vasculopathy. Am J Med Sci. 2011;342:524-6.
7. Khan TA, Cuchacovich R, Espinoza LR, Lata S, Patel NJ, García-Valladares I, et al. Vasculopathy, hematological, and immune abnormalities associated with levamisole-contaminated cocaine use. Semin Arthritis Rheum. 2011;44:5-54.
8. Álvarez H, Marino AI, García JF, Rodríguez L, Gómez I, Bermejo AM. ANCA-positive vasculitis induced by levamisoleadulterated cocaine and nephrotic syndrom: kidney as an unusual target. Am J Case Reports. 2013;14:557-61.
9. Zwang NA, van Wagner LB, Shawn R. A case of levamisole-induced systemic vasculitis and cocaine-induced midline destructive lesion. J Clin Rheumatol. 2011;17:197-200.
10. Purai N, Jain T, Bhanot R, Krishnan Natesan S. Levamisole-induced leukocytoclastic vasculitis and neutropenia in a patient with cocaine use: An extensive case with necrosis of skin, soft tissue, and cartilage. Addict Sci Clin Pr. 2012;7:1-10.
11. Sánchez-Cruz A, Marrero S, Betancourt J, Andino M, López A, Gutiérrez-Nuñez J. Cocaine induced vasculitis: Have we found a Culprit? Case Rep Rheumatol. 2012;2012:982361.

12. Crowe DR, Kim PS, Mutasim DF. Clinical, histopathologic, and immunofluorescence findings in levamisole/cocaine-induced thrombotic vasculitis. Int J Dermatol. 2013;53:635-7.
13. Restrepo CS, Carrillo JA, Martínez S, Ojeda P, Rivera AL, Hatta A. Pulmonary complications from cocaine and cocaine-based substances: Imaging manifestations. Radiographics. 2007;27(4):941-56.
14. Rivera TL, Belmont HM, Weissmann G. Systemic lupus erythematosus in 6 cocaine user at Bellevue Hospital. J Rheumatol. 2009;36:2854-5.
15. Schmidt-Acevedo S, Pérez-Romano B, Ruiz- Arguelles A. LE cells result from phagocytosis of apoptotic bodies induced by antinuclear antibodies. J Autoimmun. 2000;15:15-20.
16. Cohen PL. Apoptotic cell death and lupus. Springer Semin Immun. 2006;28:145-52.
17. Haines KA, Reibman J, Callegari PE, Abramson SB, Philips MR, Weissmann G. Cocaine and its derivatives blunt neutrophil functions without influencing phosphorylation of 47-kilodalton component of the reduced nicotinamide-adenine dinucleotide phosphate oxidase. J Immunol. 1990;144:4757-66.
18. Cervera R, Khamashta MA, Font J, Sebastiani GD, Lavilla P, Mejía JC, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: A comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003;82:299-308.