Cocaine as a trigger of systemic lupus erythematosus. A case report of alveolar hemorrhage and proliferative nephritis

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Case Report

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Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by loss of immune tolerance, autoantibody production, and immune-complex mediated tissue injury. A recently recognized entity is cocaine-induced or cocaine-associated SLE, frequently linked to levamisole-adulterated cocaine, which promotes aberrant neutrophil activation, impaired apoptotic debris clearance, and development of multiple autoantibodies. These mechanisms may trigger aggressive autoimmune phenotypes mimicking or exacerbating idiopathic SLE.

We describe the case of a 29-year-old male with chronic cocaine consumption who presented with constitutional symptoms and multisystemic involvement, including pulmonary, renal, hematologic, and serosal manifestations. Laboratory evaluation revealed pancytopenia, profound hypocomplementemia, high anti-dsDNA titers, and atypical p-ANCA positivity. Renal biopsy demonstrated class IV lupus nephritis, while bronchoalveolar lavage confirmed diffuse alveolar hemorrhage. These findings, together with recent cocaine exposure, supported the diagnosis of cocaine associated SLE an entity rarely reported in the literature and not previously documented in Mexico.

The patient required high-dose corticosteroids, cyclophosphamide induction, and renal replacement therapy. He developed hypoxemic respiratory failure requiring mechanical ventilation, with respiratory improvement following immunosuppressive therapy. This case highlights the importance of considering cocaine use as a potential trigger for severe autoimmune presentations, particularly in young patients with unexplained multisystemic inflammation. Early recognition and prompt treatment are crucial to prevent progression and irreversible organ damage.

Keywords: Systemic Lupus erythematosus, Alveolar hermorrhage, nephritis.

Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting millions of people worldwide[1], with a clinical presentation capable of involving virtually any organ system. Its diagnosis is currently based on the SLICC criteria proposed in 2012[2], which integrate clinical expression with a more robust immunologic profile[3] and allow cumulative classification. This approach increases diagnostic sensitivity and facilitates early identification of patients with initial or atypical manifestations.

Timely recognition of SLE is essential, as medium-term survival is favorable when the disease is detected and treated early[4]. However, the development of lupus nephritis remains one of the principal determinants of poor prognosis[5,6] as it significantly reduces long-term survival and increases the risk of irreversible organ damage.

From a pathophysiological standpoint, SLE is characterized by failures in mechanisms of immune tolerance[7], particularly in the elimination of autoreactive lymphocytes and the clearance of nuclear antigens. These defects allow the persistence of autoantigens within the extracellular microenvironment, triggering abnormal immune responses and the production of pathogenic autoantibodies that cause progressive tissue injury[8].

Several exogenous substances have been implicated as modulators or triggers of autoimmunity. Among them, chronic cocaine use has been identified as a potential facilitator of aberrant immune responses[9]. Prolonged exposure may significantly impair phagocytic function, interfere with the production of effector molecules, and alter mechanisms of neutrophil adhesion and aggregation[10]. These effects, which require repeated and sustained

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Table 1 – Autoimmunity Study in the Patient

Autoimmunity	Results
Anti-dsDNA (IgG)	258 UI/mL
Antinuclear	> 1:320
Complement C3	36
Complement C4	10
Anti-MBG	2.8
Antibody anti-Myeloperoxidase (MPO)	< 2.0 UR/ml
P-Anca atypical	1:160
Myeloperoxidase	< 2.0
Antiprotease3	< 2.0
Hepatitis B surface antigen	Neg
Hepatitis C antibody	Neg
IgM anti-core antibody	Neg

exposure, may promote a dysfunctional immunologic milieu and, in exceptional cases, contribute to the development or exacerbation of autoimmune disease.

In this context, we present the case of a patient with SLE associated with chronic cocaine use. This type of presentation is unusual, occurs predominantly in males, and its true incidence remains unknown due to the limited number of cases reported. To our knowledge, this represents the first documented case in Mexico and the third described in the international literature[11], underscoring the importance of considering substance use as a potential factor in atypical clinical scenarios of autoimmunity.

Case report

We present the case of a 29-year-old male with a significant history of frequent cocaine use since the age of 16 (approximately 3 g per day), with his most recent use occurring one day prior to presentation.

He sought medical attention for a three-week history of progressive dyspnea, classified as grade 3/4 according to the modified Medical Research Council scale, associated with dry cough and bilateral pleuritic chest pain rated 9/10 in intensity. The clinical picture was accompanied by facial edema, asthenia, and adynamia. He also reported occasional episodes of gross hematuria with foamy urine, eventually progressing to anuria.

Upon arrival, elevated blood pressure values were documented (systolic readings around 170/100 mmHg). Physical examination revealed facial edema, bibasilar wheezing, inspiratory crackles, and lower-extremity edema. No signs of synovitis, joint stiffness, deformities, or enthesis's were identified.

Laboratory studies showed pancytopenia, hypoalbuminemia, hypercholesterolemia, and elevated nitrogenous waste products. Urinalysis demonstrated

Table 2. Clinical manifestations

Lupus manifestations	Results
Age at diagnosis	29 years
Ethnicity	mestizo
Malar erythema	–
Photosensitivity	–
Discoid lupus	–
Oral ulcers	–
Serositis	+
Arthritis	–
Renal involvement	+
Diffuse alveolar Hemorrhagic	+
CNS involvement	–
Leukopenia	+
Lymphopenia	+
Anemia	+
Thrombocytopenia	+
Antibodies	
ANA	+
Anticardiolipin	–
Anti-DNA	+
ANCAS	
c-ANCA	–
p-ANCA	+
Complement C3	Consumed
Complement C4	Consumed

nephrotic-range proteinuria, both upper and lower tract hematuria, pyuria, and urinary sediment with hematic and granular casts. The 24-hour urine protein excretion was 8 g. Renal ultrasound revealed enlarged kidneys with preserved corticomedullary differentiation. Given the presence of arterial hypertension, upper-tract hematuria, and renal function impairment with preserved morphology, a diagnosis of rapidly progressive glomerulonephritis was considered. Autoimmune testing was subsequently performed (Table 1).

Chest computed tomography without contrast revealed diffuse ground-glass opacities throughout both lungs, predominantly in the central regions, consistent with pulmonary edema. A right pleural effusion of approximately 10% was noted, along with global cardiomegaly and a pericardial effusion measuring 2.1 cm in thickness (Fig. 1)

Based on the clinical findings including positive antinuclear and anti-dsDNA antibodies, hypocomplementemia, and hematologic, respiratory, and renal abnormalities, as well as the presence of polyserositis a diagnosis of active systemic lupus erythematosus (SLE) was established, with a SLEDAI-2K score of 21 points. A probable etiologic association with cocaine use, likely adulterated with levamisole (as reported by the patient), was also considered.

Given the high degree of disease activity, particularly due to renal involvement, treatment was initiated with methylprednisolone 1 g/day for three

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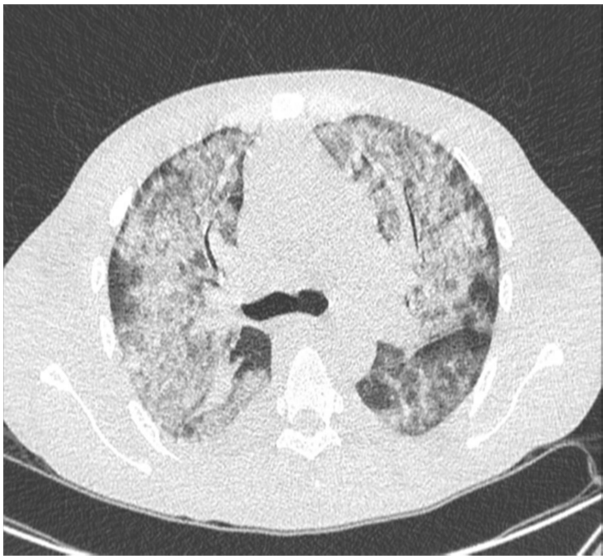

Figure 1. Chest CT showing diffuse bilateral ground-glass opacities, right pleural effusion (10%), global cardiomegaly, and pericardial effusion measuring 2.1 cm.

days, followed by prednisone 1 mg/kg/day and chloroquine 250 mg/day. Because of the rapid deterioration in renal function, renal replacement therapy was started, and a kidney biopsy was performed to classify the lupus involvement and determine the need for induction therapy.

Histopathology revealed class IV lupus nephritis (Fig. 2). Based on these findings, immunosuppressive therapy with cyclophosphamide at a dose of 15 mg/kg was initiated.

The respiratory manifestations progressed to hypoxemic respiratory failure, requiring invasive mechanical ventilatory support. The diagnosis of diffuse alveolar hemorrhage was confirmed by bronchoalveolar lavage, which showed persistently hemorrhagic aliquots. Following immunosuppressive therapy, the patient exhibited both clinical and radiologic improvement, allowing successful extubation without complications.

The patient presented with severe dyspnea, pleuritic pain, facial edema, pancytopenia, nephrotic-range proteinuria, and profound hypocomplementemia. Autoantibody testing showed ANA >1:320, anti-dsDNA positivity, and atypical p-ANCA. CT imaging demonstrated bilateral ground-glass opacities, pleural effusion, and pericardial effusion. Bronchoalveolar lavage confirmed diffuse alveolar hemorrhage. Renal biopsy revealed class IV lupus nephritis with activity index 5 and chronicity index 9. High-dose corticosteroids and cyclophosphamide were initiated, leading to respiratory improvement and successful extubation. Renal prognosis remained guarded.

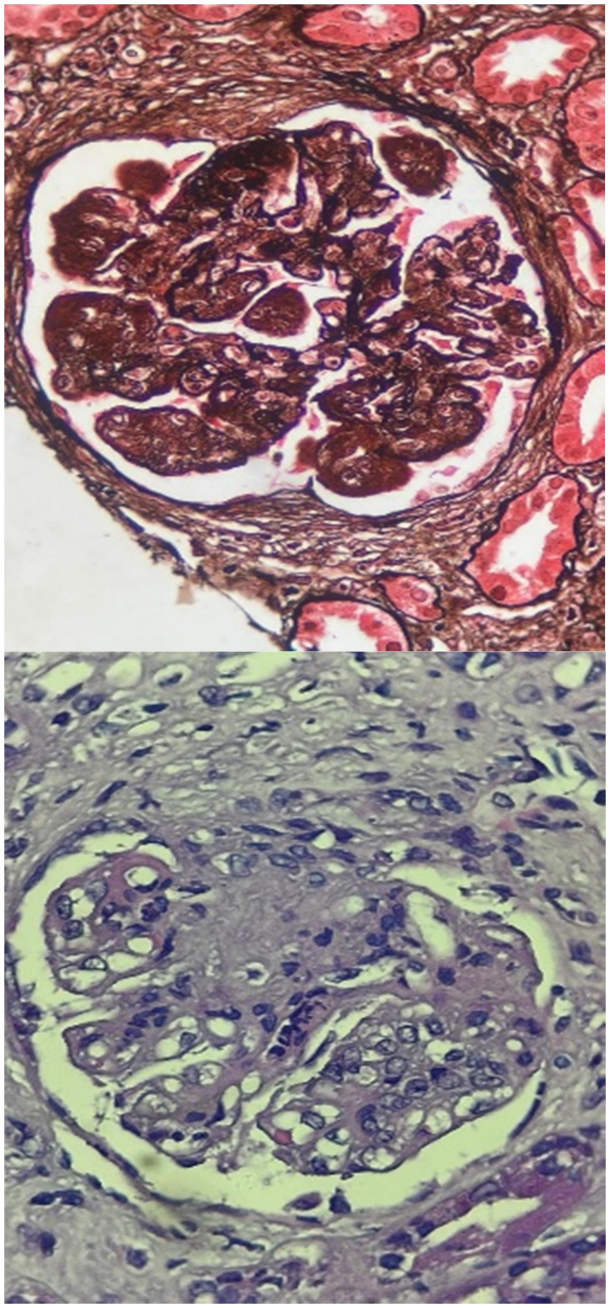

Figure 2. Renal biopsy demonstrating diffuse active/chronic class IV (A/C) ISN/RPS lupus nephritis, activity index 5, chronicity index 9, with 30% interstitial fibrosis and 30% tubular atrophy.

Discussion

Cocaine use represents a growing problem in Latin America, not only because of its addictive potential but also due to its systematic adulteration with levamisole, an immunomodulatory drug capable of inducing profound alterations in immune function[1,3]. Several studies have identified levamisole in up to two-thirds of seized samples[4], a finding that has

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expanded the spectrum of diseases associated with its consumption. In this context, chronic often unrecognized exposure may trigger autoimmune manifestations that mimic or precipitate systemic lupus erythematosus (SLE)[5].

The pathophysiology of levamisole induced SLE differs partially from idiopathic SLE. Whereas the classic disease is driven by defective clearance of nuclear antigens and persistence of autoreactive lymphocytes[6,8], levamisole enhances neutrophil activation pathways, stimulates MPO/PR3 dependent inflammatory cascades, and promotes the formation of multiple autoantibodies, including ANA, anti-dsDNA, p-ANCA, and ant histone antibodies[9,12]. These alterations, coupled with the direct endothelial and pulmonary toxicity of cocaine[13], create an immunologic microenvironment prone to exaggerated autoimmunity.

In the case we present, the patient exhibited a particularly aggressive phenotype characterized by pancytopenia, profound hypocomplementemia, class IV lupus nephritis, and diffuse alveolar hemorrhage (DAH). This pattern partially aligns with international reports describing renal involvement and cytopenia's in chronic users of levamisole-adulterated cocaine[14,15]; however, the simultaneous presence of diffuse proliferative nephritis and DAH is uncommon and suggests a mixed process in which autoimmunity and direct toxicity converge[17].

The pulmonary injury observed in our patient acute respiratory failure, need for invasive mechanical ventilation, and bronchoalveolar lavage showing clearly hemorrhagic aliquots correlates with two main mechanisms:

- **cocaine induced endothelial injury**, driven by vasospasm, disruption of the alveolar capillary membrane, and focal necrosis[13,18];
- **immune mediated inflammation,** characteristic of SLE, leading to capillarity's and vascular fragility.

This combination favors the development of DAH, a potentially fatal complication that in this case resolved with intensive immunosuppressive therapy and ventilatory support[20].

Regarding renal involvement, the finding of class IV lupus nephritis is consistent with the high autoimmune burden evidenced in serologic studies: ANA >1:320, markedly elevated anti-dsDNA, and severely depleted complement levels (C3: 36 mg/dL; C4: 10 mg/dL). The presence of an atypical p-ANCA (1:160), despite negative MPO/PR3, aligns with the profile described in levamisole-related cases[10,15] where non-conventional ANCA patterns predominate, often associated with necrotizing vasculitis or proliferative glomerulopathies. The coexistence of both processes explains the rapid progression to anuria and the early need for renal replacement therapy.

When comparing this case with published reports, similarities emerge regarding age at presentation (20–45 years), male sex, severe cytopenia's, multiple autoantibodies, and renal involvement[4,15]. However, few cases have documented the triad of active SLE + diffuse proliferative nephritis + diffuse alveolar hemorrhage, which distinguishes this patient within the spectrum of cocaine associated SLE and likely places him among the most severe forms of this emerging entity. Furthermore, according to the consulted literature, this appears to be the first documented case in Mexico and among the few reported in Latin America, underscoring the epidemiological importance of recognizing this diagnosis in populations with high prevalence of adulterated cocaine use.

From a pathophysiological perspective, the interaction between levamisole, cocaine, and autoimmunity is central to understanding the course of this case. Cocaine increases cellular apoptosis, impairs phagocytosis[13], and generates persistent nuclear debris; levamisole interferes with immune clearance[10,12] and stimulates autoantibody production; and SLE amplifies endothelial damage and lymphocytic activation. The result is an immunologic storm that rapidly compromises target organs (Table 2).

Timely treatment with methylprednisolone pulses, followed by dose-adjusted cyclophosphamide, was essential to control the inflammatory activity. Absolute cessation of cocaine use constitutes the cornerstone of the therapeutic approach, as ongoing exposure can perpetuate immunologic injury and prevent remission. Despite the initial severity, the patient's respiratory course improved favorably, allowing successful extubation on the seventh day; however, the renal prognosis will depend on the response to induction therapy and strict adherence to abstinence and nephrology follow-up.

Conclusion

In conclusion, this case illustrates how the combination of cocaine adulterated with levamisole can trigger unusually aggressive presentations of systemic lupus erythematosus, with rapidly progressive simultaneous pulmonary and renal involvement. Recognition of this association is crucial for establishing an early diagnosis, initiating appropriate treatment, and preventing potentially fatal complications. Its identification is particularly relevant in regions where cocaine use is prevalent and where levamisole adulteration has become widespread.

This case illustrates how chronic cocaine use, possibly adulterated with levamisole, can trigger an aggressive presentation of systemic lupus erythematosus, characterized by severe renal involvement and diffuse alveolar hemorrhage. Early

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recognition of this association is essential, particularly in young patients with a history of substance use and unexplained autoimmune manifestations. Timely identification allowed the initiation of appropriate immunosuppressive therapy and life-support measures, resulting in a favorable respiratory outcome. This case underscores the importance of considering cocaine use as a potential trigger in atypical and clinically severe autoimmune presentations.

Conflicts of interests

The authors declare no conflict of interest.

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