Clinical Profile of Levamisole-Adulterated Cocaine-Induced Vasculitis/Vasculopathy

A 30-Case Series

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Objectives: The aims of this study were to describe clinical and laboratory manifestations of patients with levamisole-adulterated cocaine-induced vasculitis/vasculopathy and to propose a skin classification according to the distribution and severity of lesions.

Methods: We report the characteristics of 30 patients admitted with levamisole-adulterated cocaine-induced vasculitis/vasculopathy in 4 high-complexity institutions in Colombia, from December 2010 to May 2017. We compare our findings with the principal published series.

Results: Median age was 31 years (interquartile range, 27–38 years) with a male-to-female ratio of 5:1. Eighty-three percent of the patients had retiform purpura affecting the limbs, buttocks, face, or abdomen; 73% had ear necrosis, 50% cutaneous ulcers, 17% genital necrosis, 13% oral ulcers, and 10% digital necrosis. Cutaneous involvement was classified according to the frequency of the compromised corporal area, and purpuric lesions were stratified in 4 grades of severity. Anti–neutrophil cytoplasmic autoantibodies were positive in 85% of the cases, lupus anticoagulant in 73%, and antinuclear autoantibodies in 57%, and rheumatoid factor was negative in all cases. We found nephritis in 17 cases (57%). Prednisolone was used in most of the patients (70%), with other immunosuppressive agents being used in a lower percentage. Improvement was observed in 93% of the patients, but symptoms recurred in 40%, attributed to relapses in consumption. End-stage chronic renal disease developed in 10% of the cases, and 1 patient died.

Conclusions: Because of rising cocaine consumption and levamisole adulteration frequency, levamisole-adulterated cocaine-induced vasculitis/vasculopathy is becoming more common. Detailed characterization of skin involvement coupled with multiple antibody positivity is essential for a diagnosis. Renal involvement is frequent, clinically and histologically heterogeneous, and potentially serious.

Key Words: anti–neutrophil cytoplasmic antibody, cocaine, levamisole, nephritis, purpura

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According to the United Nations Office on Drugs and Crime, there were 18.3 million cocaine users worldwide in 2016.[1] The most frequent added substances to cocaine were hydroxyzine, diltiazem, and levamisole.[2] Levamisole was formerly used as an antihelminthic and immunomodulatory agent, but currently, it is the third most used cocaine adulterant in Colombia.[3] It was first detected by the Drug Enforcement Administration in 2003 in cocaine blocks, and by July 2009, it was present in 69% of confiscated cocaine at the borders of the United States.[4] The first reported cases of agranulocytosis associated with levamisole-adulterated cocaine appeared in 2009,[5] and in 2010 the first reports of vasculitis with cutaneous involvement.[6]

Because of the high frequency of cocaine contamination with levamisole in different parts of the world, several hypotheses about its role as an adulterant have been proposed. There were descriptions of its effect on the central nervous system as an antidepressant and mood modulator when it was used as an antihelminthic agent.[7] Animal studies (in dogs and guinea pigs) have demonstrated inhibition of type A monoamine oxidase, inhibition of serotonin reuptake,[8] and as a nicotinic receptor agonist and allosteric modulator of these receptors.[9] Likewise, it has been proposed that it could enhance the pleasure effects and dependency of cocaine, because of its agonist effects on central nicotinic receptors and by stimulating glutamatergic activity in the dopaminergic neurons that are involved in reward mechanisms in the mesolimbic system.[10]

Its short plasmatic life, rapid absorption and elimination, its physical and psychotropic characteristics, and the difficulty for its detection have made levamisole an ideal adulterant for cocaine, augmenting its weight and quantity with cost reduction and higher profit margins. Actual standardized tests for levamisole detection are not widely distributed; there are liquid chromatography/mass spectrometry methods available in specialized laboratories, although the results can be negative if the procedure is done more than 24 hours after the exposition. Two hospital case series detected the presence of levamisole in 68% to 88% of cocaine-positive urine samples.[11,12]

Besides its use as an antiparasitic, levamisole has also been used in recurring and chronic skin, mucous membrane, eye, and respiratory tract infections by viruses, bacteria, and fungi; in inflammatory chronic diseases, such as nephrotic syndrome, especially in children[13]; systemic lupus erythematosus (SLE)[14]; Crohn disease[15]; reactive arthritis; rheumatoid arthritis; and malignances such as leukemia, breast cancer, sarcomas, and melanoma.[16] New treatment alternatives and the evidence of hematologic adverse effects led to withdrawal from the market in the United States by the year 2000, although it is still commercialized as an antihelminthic for veterinarian use.[17]

Until now, the clinical data of more than 50 patients with levamisole-cocaine vasculopathy have been published[18-24] including 16 Colombian patients.[25-28] Although determination of cocaine

in urine is not described in all published cases, all patients acknowledged recent use of the drug, including those from the Colombian series.

We describe a case series of 30 Colombian patients with levamisole-adulterated cocaine-induced vasculitis/vasculopathy and propose a new retiform purpura classification.

MATERIALS AND METHODS

Patients

We describe the clinical and laboratory characteristics of 30 Colombian patients with levamisole-cocaine vasculopathy who were admitted to the rheumatology services of Hospital Universitario San Vicente Fundación de Medellín, IPS Universitaria Clínica León XIII de Medellín, Hospital General de Medellín, and Clínica de Artritis Temprana de Cali between December 2010 and May 2017. We compared the data with the main published series available in PubMed and EMBASE. We propose a new classification of cutaneous involvement describing its distribution and stratifying retiform purpura in 4 grades according to its severity and extension, including the size of individual lesions. The ethics committee of the participating institutions approved this research.

Statistical Analysis

For qualitative variables, a frequency analysis was made. For quantitative variables, median was used as central tendency measurement and interquartile range (IQR) as dispersion measurement. A relationship between qualitative and quantitative variables was examined by Mann-Whitney *U* test. We considered $P < 0.05$ as statistically significant. All the data were analyzed in Epidat 4.2 and SPSS 22.0 (Licensed by Universidad CES, Medellín, Colombia).

RESULTS

Clinical Data

All patients were mestizo with a median age of 31 years (IQR, 27–38 years); 83% were male, with a male-to-female ratio of 5:1. Inhalation was the only consumption route, and recent consumption was reported in all the cases; In addition, 70% of the patients consumed marijuana, 63% tobacco, 63% alcohol, 7% opioids, and 3% inhaled glue. The median time from initial symptoms to diagnosis was 12 months (IQR, 6–24 months). Urinary cocaine levels were not measured in all patients at admission, but features of the presented cases provide enough evidence to link these with levamisole contamination of cocaine. Levamisole levels were not measured because of lack of an available test in our institutions.

The most frequent clinical manifestations were cutaneous lesions, with 73% having ear necrosis and 83% with retiform purpura affecting mainly the extensor part of the superior limbs, inferior limbs, buttocks, face, and abdomen; the involvement of other areas was less frequent (Fig. 1). Retiform purpura was classified in 4 grades according to severity and extension (Fig. 2).

Most of the patients had extracutaneous manifestations, with nephritis being one of the most common (57% of the cases), followed in frequency by joint symptoms (40%) and fever (23%) (Fig. 3). Two patients had diffuse alveolar hemorrhage, none of whom required intubation. The characteristics of our patients are compared with those of other published series in Table 1.

Laboratory Data

We found anemia in 73% of the patients, lymphopenia in 70%, leukopenia in 28%, thrombocytosis in 23%, neutropenia in 17%, autoimmune hemolytic anemia in 10%, and thrombocytopenia in 10%.

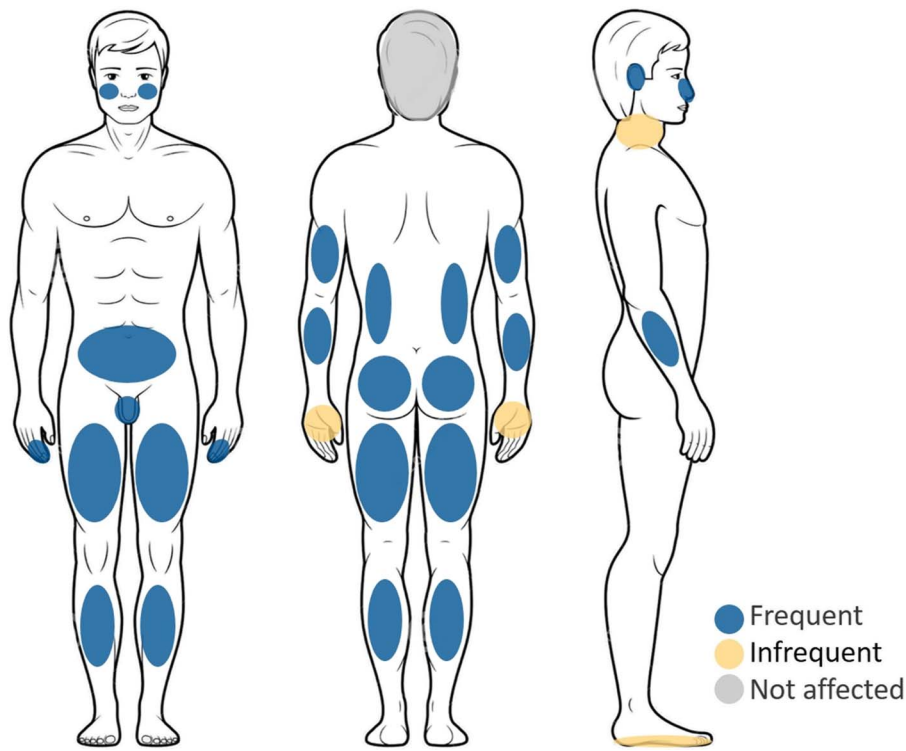

FIGURE 1. Distribution of cutaneous involvement in levamisole-adulterated cocaine-induced vasculitis/vasculopathy. The absence of scalp involvement and low frequency of palmar and plantar compromise are highlighted. Modified from es.dreamstime.com (no attribution required). Color online-figure is available at http://www.jclinrheum.com.

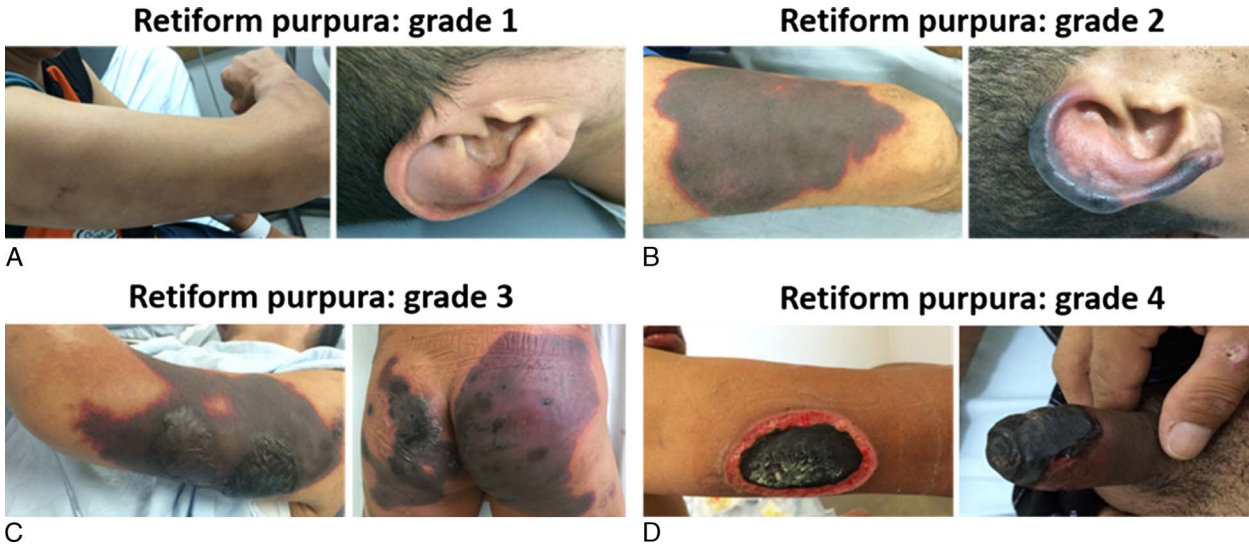

FIGURE 2. Levamisole-adulterated cocaine-induced vasculitis/vasculopathy–associated retiform purpura classification. A, Grade 1: livedo reticularis or racemosa with incipient purpura (individual lesions ≤1 cm). B, Grade 2: more extended purpuric lesions, sometimes confluent (individual lesions >1 cm). C, Grade 3: purpuric lesions in the presence of hemorrhagic blisters. D, Grade 4: deep purpuric lesions with associated ulceration. Photographs taken from our reported cases. Color online-figure is available at http://www.jclinrheum.com.

Acute-phase reactants were elevated in all patients with a median for erythrocyte sedimentation rate of 60 mm/h (IQR, 49–89 mm/h) and for C-reactive protein of 6.3 mg/dL (IQR, 3.5–12.6 mg/dL).

Anti–neutrophil cytoplasmic autoantibodies (ANCAs) were positive in 85% of the patients by either indirect immunofluorescence or enzyme-linked immunosorbent assay; 93% with perinuclear pattern (p-ANCA) and 7% with mixed p-ANCA and cytoplasmic (c-ANCA) patterns, with titers raging from 1:40 to 1:2560; 57% were directed against both myeloperoxidase (anti-MPO) and proteinase 3 (anti-PR3), and 43% had anti-MPO alone. None of the patients had an isolated c-ANCA or anti-PR3. Lupus anticoagulant (LA) was positive in 73% of the cases, with immunoglobulin M (IgM) anticardiolipin (aCL) in 24% and IgG aCL in 14% (both with positivity in moderate titers); and 15% had anti–β_2-glycoprotein I. Antinuclear antibodies (ANAs) were positive in 57%, with titers raging from 1:40 to 1:1280, with a homogenous pattern in most of the cases; Anti-dsDNA was positive in 35%, with titers raging from 1:10 to 1:160. Only 2 patients had positive anti-Ro, with the rest of the extractable nuclear autoantibodies being negative. Cryoglobulins were positive in only 1 case, and the rheumatoid factor was negative in all the patients. We found hypocomplementemia in 57% of the cases (Fig. 4).

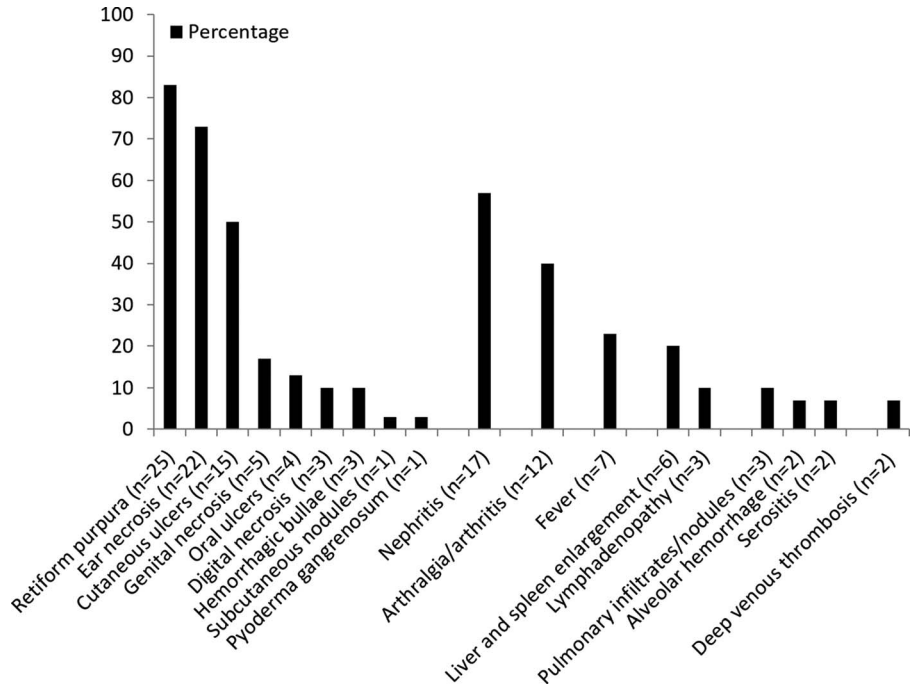

FIGURE 3. Clinical findings. Retiform purpura and ear necrosis were the most frequent clinical findings.

TABLE 1. Clinical Characteristics of Levamisole-Cocaine Vasculopathy in Colombia and in Other International Case Series

	Muñoz-Vahos et al. (Present Study)	McGrath et al.[18]	Chung et al.[19]	Graf et al.[20]	Ullrich et al.[21]	Gross et al.[22]	Khan et al.[23]	Poon et al.[24]
n	**30**	**18**	**6**	**6**	**5**	**4**	**4**	**4**
Age, median (IQR), y	31 (27–38)	47 (42.5-51.5)	46 (37–50)	44.5 (39.6-48.5)	45 (28–52)	46 (46–56.7)	49.5 (46.3–54.3)	48.5 (47.5–56.5)
Male/female relation, n	25/5	7/11	2/4	0/6	1/4	2/2	2/2	3/1
Retiform purpura, %	83	33.3	100	100	100	100	100	75
Ear necrosis, %	73	27	100	100	60	75	75	75
Cutaneous ulcers, %	50	22	0	100	0	0	50	25
Genital necrosis, %	17	0	0	0	0	0	0	0
Oral ulcers, %	13	22.2	0	0	0	0	0	50
Digital necrosis, %	10	0	0	0	0	0	0	0
Hemorrhagic bullae, %	10	5.5	16.7	0	20	50	0	25
Subcutaneous nodules, %	3	0	0	0	20	0	0	0
Nephritis, %	57	44.4	0	0	0	0	0	0
Arthralgia/arthritis, %	40	83	0	0	80	75	50	75
Fever, %	23	44.4	0	0	40	0	100	75
Lymphadenopathy, %	10	0	0	0	0	0	0	25
Liver and spleen enlargement, %	20	0	0	0	0	0	25	0
Pulmonary infiltrates/nodules, %	10	22.2	0	0	40	0	0	0
Alveolar hemorrhage, %	7	17	0	0	0	0	0	0
Serositis, %	7	0	0	0	0	0	0	0
DVT, %	7	0	0	0	0	0	0	0

DVT indicates deep vein thrombosis.

There were 17 patients with renal involvement; 35% had elevations in serum creatinine, with a median of 1.85 mg/dL (IQR, 1.2–5.3 mg/dL), 3 of whom required dialysis; 71% had proteinuria, with a median of 716 mg/d (IQR, 280–4600 mg/d), with 42% in nephrotic range; hematuria was present in 88%, and pyuria and cylindruria in 41%. Ear necrosis ($P = 0.038$), genital necrosis ($P = 0.035$), anemia ($P = 0.038$), and ANCA positivity ($P = 0.016$) were associated with the presence of nephritis.

In all patients, active infections with human immunodeficiency virus, syphilis, and hepatitis B and C viruses were discarded. Laboratory findings are compared with other published series in Table 2.

Histopathology

Cutaneous

Skin biopsy was obtained in 21 patients (70%), finding leukocytoclastic vasculitis (24%), pseudovasculitis (19%), thrombotic vasculopathy with leukocytoclastic vasculitis (19%), thrombotic vasculopathy with pseudovasculitis (19%), and pyoderma gangrenosum with vasculopathy (5%) (Fig. 5). We compared these findings with those of other series, as shown in Table 3.

Renal

Renal biopsies were performed in 8 of the 17 patients with renal involvement (27%), with membranous glomerulonephritis (37.5%) and immune complex–mediated proliferative glomerulonephritis (25%) being the most frequent, followed by C3-mediated proliferative glomerulonephritis (12.5%), pauci-immune proliferative glomerulonephritis (12.5%), and focal and segmental glomerulosclerosis (12.5%) (Fig. 6).

Treatment

Cessation of cocaine consumption was ordered in all the cases during medical attention. Pharmacological treatment was given in 83% of the patients; most of them (70%) were administered prednisolone with a median daily dose of 50 mg (IQR, 25–60 mg).Of the patients who received prednisolone, 28% had histological evidence of cutaneous vasculitis, and 33% of glomerulonephritis; 13% received methylprednisolone pulses, and 30% received an additional immunosuppressive drug: azathioprine (33%), chloroquine (33%), cyclophosphamide (33%), methotrexate (22%), or rituximab (11%). In addition, 20% received acetylsalicylic acid, and 17% received warfarin. Despite limitations with follow-up, there was an improvement in 93% of the patients, but with 40% of the patients relapsing because of resumed consumption, and 1 patient died because of infection. Three patients (10%) developed end-stage chronic renal disease (ESRD), from 0 to 24 months after diagnosis, with their biopsies showing C3-mediated proliferative glomerulonephritis, membranous glomerulonephritis, and immune complex–mediated proliferative glomerulonephritis. The comparison with other series is described in Table 4.

DISCUSSION

We present the clinical and laboratory data of 30 Colombian patients with levamisole-cocaine vasculopathy who were admitted to 4 high-complexity institutions, being to our knowledge the largest series published to date. In comparison to other series, our patients were younger at diagnosis, most of them were men, and they had lower frequency of hematologic manifestations, although renal involvement was more common. We also found unusual manifestations such as alveolar hemorrhage and macrovascular thrombosis (Table 1).

As it has been clearly described in the literature, we confirm in our series that cutaneous involvement is the most frequent clinical manifestation, with retiform purpura and ear necrosis being the most common findings.[29] Nevertheless, this finding has been reported in other diseases that generate microvascular thrombotic occlusion such as antiphospholipid syndrome (APS),[30] anticoagulant-associated necrosis,[31] and disseminated intravascular

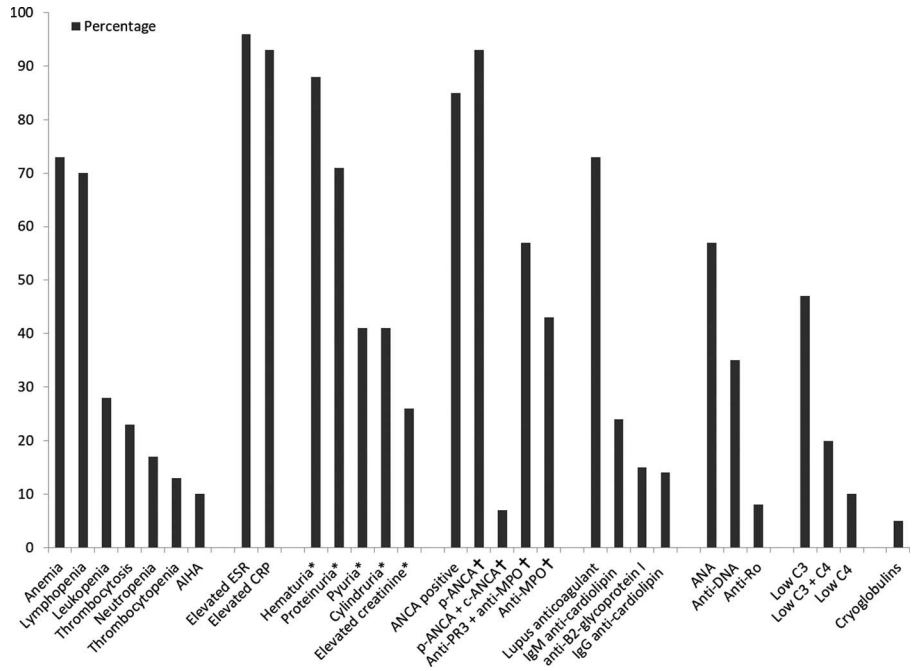

FIGURE 4. Laboratory findings. Most of the patients had multiple autoantibody positivity. Hematologic and renal involvements were frequent. AIHA indicates autoimmune hemolytic anemia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. *Percentage in relation to the patients with nephritis. †Percentage in relation to ANCA-positive patients.

TABLE 2. Comparison of Laboratory Findings in Different Case Series

	Muñoz-Vahos et al. (Present Study)	McGrath et al.[18]	Chung et al.[19]	Graf et al.[20]	Ullrich et al.[21]	Gross et al.[22]	Khan et al.[23]	Poon et al.[24]
Anemia	73	NA	NA	NA	NA	25	NA	NA
AIHA	10	NA	NA	NA	NA	NA	NA	NA
Leukopenia	28	28	0	NA	80	50	75	75
Neutropenia	17	22.2	NA	66.7	60	25	75	75
Thrombocytosis	23	NA	NA	NA	NA	0	NA	NA
Elevated CRP	93	NA	50	100	NA	NA	100	NA
Elevated ESR	96	NA	100	100	NA	50	100	NA
Elevated creatinine[a]	35	27.8	NA	NA	NA	NA	NA	NA
Proteinuria[a]	71	87.5	NA	NA	NA	NA	NA	NA
Hematuria[a]	88	75	NA	NA	NA	0	NA	NA
Pyuria[a]	41	NA	NA	NA	NA	0	NA	NA
Cylindruria[a]	41	37.5	NA	NA	NA	0	NA	NA
ANCA positive	85	100	NA	100	100	100	100	100
p-ANCA[b]	93	50	83.3	100	80	NA	100	75
c-ANCA[b]	0	0	0	0	20	NA	0	25
p-ANCA + c-ANCA[b]	7	50	16.7	0	0	NA	0	0
Anti-MPO[b]	43	50	0	16.7	0	25	0	50
Anti-PR3[b]	0	0	0	16.7	20	0	25	50
Anti-PR3 + anti-MPO[b]	57	50	100	66.7	80	75	0	0
LA	73	66.7	NA	NA	80	100	75	NA
IgM-aCL	24	NA	100	NA	80	NA	50	NA
IgG aCL	14	NA	NA	NA	0	NA	NA	NA
Anti–β_2-glycoprotein I	15	NA	NA	NA	20	NA	NA	NA
ANAs	57	82.3	33.3	100	80	100	100[c]	0
Anti-dsDNA	35	33.9	0	0	NA	0	NA	NA
Anti-Ro	8	NA	0	NA	NA	0[d]	NA	NA
Rheumatoid factor	0	NA	NA	NA	0	0	NA	0
Low C3	47	NA	0	NA	0	0	NA	0
Low C4	10	NA	0	NA	0	25	NA	0
Low C3 + C4	20	NA	0	NA	100	25	NA	0
Cryoglobulins	5	NA	0	0	0	0	NA	25

Values are presented as percentages.

[a]Percentage of the total of patients with nephritis.

[b]Percentage of the total of patients with ANCA positivity.

[c]Only measured in 1 of the 4 patients.

[d]One anti-RNP–positive patient.

AIHA indicates autoimmune hemolytic anemia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NA, not available.

coagulation[32]; embolic occlusion as in infective endocarditis[33] and fat embolism[34]; infective bacterial,[35] fungal,[36] or parasitic[37] occlusion; or primary vasculitis such as polyarteritis nodosa,[38] ANCA-associated vasculitis (AAV),[39] and cryoglobulinemic vasculitis,[40] making the awareness of the typical pattern and distribution of skin involvement a necessity for correct diagnosis. The distribution of the cutaneous lesions according to the observed frequency in our patients and by description of other authors[29] is represented in Figure 1. Gillis et al.[41] classified skin findings according to severity in 3 stages; we propose a modification to this classification describing the frequency of cutaneous involvement and stratifying retiform purpura in 4 grades according to its severity and extension, including the size of individual lesions (Figs. 1 and 2). We aim to define the requirement of immunosuppressive treatment by limiting it to only grades 3 and 4, which would probably take longer to heal and have the worst prognosis without pharmacological treatment. Prospective and larger studies are needed to confirm our hypothesis and validate this classification.

Although cutaneous ulcers are generally a consequence of an advanced degree of ischemia, we had a case of pyoderma gangrenosum with histological confirmation, which has been reported by other authors and has to be kept in mind for an adequate course of treatment.[42] Other forms of serious skin involvement found in this series included isolated or multiple digital necrosis, requiring amputation in some cases, and genital necrosis in a percentage greater than previously reported.[43,44] Most of the patients had a skin biopsy, but we did not find a clear association between the histological findings, the skin manifestations, and the positivity for APS antibodies. Although there is no solid evidence for platelet antiaggregation in this disease, it could be useful in cases where thrombotic vasculopathy is found, but this must be evaluated in further studies.

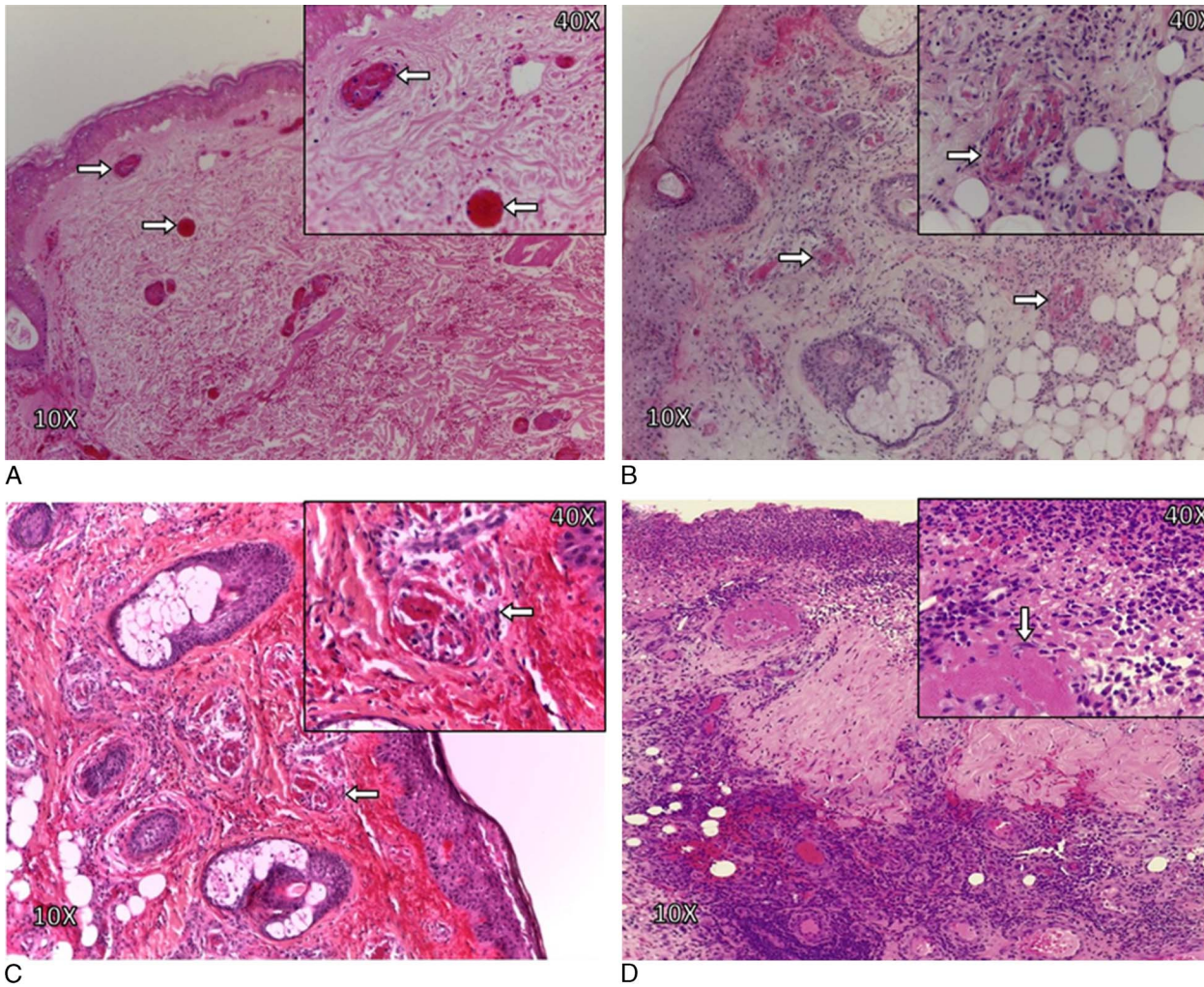

FIGURE 5. Skin biopsies. A, Thrombotic vasculopathy (hematoxylin-eosin [HE]): multiple small vessels with thin walls and thrombosis (arrows), without inflammation (dermic silence). Box: vascular thrombi details (arrows). B, Leukocytoclastic vasculitis (HE): small vessels with fibrinoid necrosis, thrombosis, polymorphonuclear neutrophil (PMN) nuclear debris, and extravasation of red blood cells (arrows). Box: vessel detail (arrow). C, Pseudovasculitis (HE): fibrinoid deposits on the wall, with scarce perivascular inflammatory infiltration (arrow). Box: vessel detail (arrow). D, Pyoderma gangrenosum (HE): superficial ulcer with a PMN-rich dense dermic inflammatory infiltration in the superior dermis (asterisk). Box: inflammatory infiltration detail (asterisk) and pseudovasculitic changes (arrows). Color online-figure is available at http://www.jclinrheum.com.

TABLE 3. Comparison of Skin Biopsy Findings

	Muñoz-Vahos et al. (Present Study)	McGrath et al.[18]	Chung et al.[19]	Graf et al.[20]	Ullrich et al.[21]	Gross et al.[22]	Khan et al.[23]	Poon et al.[24]
Cutaneous biopsy, n	21	7	6	6	3	4	3	3
Thrombotic vasculopathy, %	14	28.5	33.3	33.3	0	0	33.3	33.3
Leukocytoclastic vasculitis, %	24	42.9	16.7	0	33.3	25	0	0
Pseudovasculitis, %	19	0	0	0	0	0	0	0
Thrombotic vasculopathy + leukocytoclastic vasculitis, %	19	0	33.3	66.7	66.7	75	66.7	33.3
Thrombotic vasculopathy + pseudovasculitis, %	19	0	0	0	0	0	0	33.3
Pyoderma gangrenosum + vasculopathy, %	5	0	0	0	0	0	0	0
Panniculitis, %	0	14.3	0	0	0	0	0	0
Panniculitis + vasculitis, %	0	0	16.7	0	0	0	0	0
Necrosis, %	0	14.3	0	0	0	25	33.3	66.7

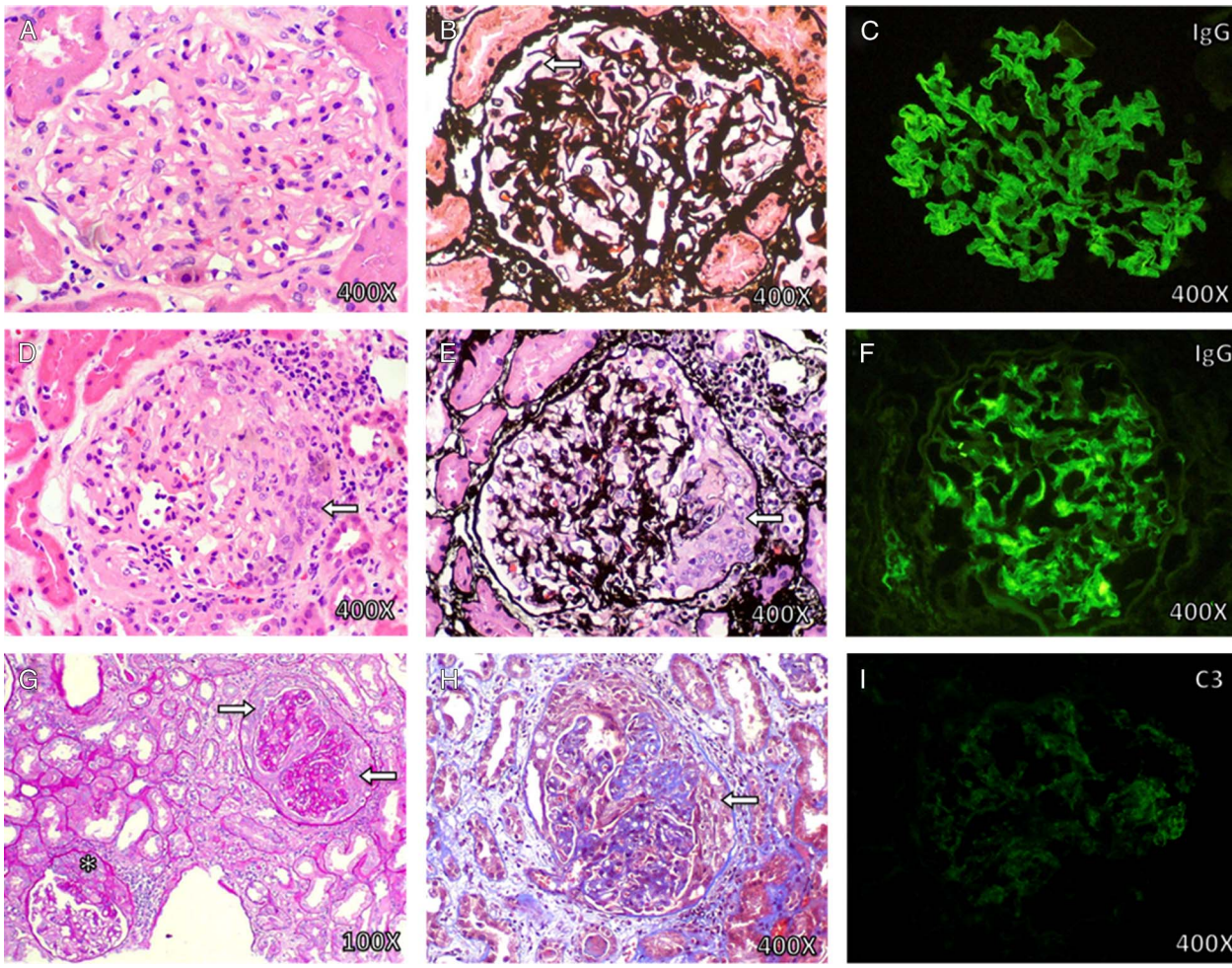

FIGURE 6. Renal biopsies. A, Membranous glomerulonephritis (HE): glomerulus with thickened capillary walls and some areas with mild increase in mesangial cellularity. B, Gomori-Grocott methenamine silver stain (GMS): the capillary wall thickening is more obvious, with some basal perpendicular projections or spikes (arrow). C, Direct immunofluorescence (DIF): strong and diffuse IgG deposits on the capillary walls. Strong and diffuse staining for IgG2 and weak for IgG3 and IgG4. D, Immune complex–mediated extracapillary focal necrotizing glomerulonephritis (HE): endocapillary proliferation, more noticeable on the right segment of the glomerulus, next to an epithelial crescent (arrow). E, GMS: capillary wall rupture adjacent to the crescent (arrow). F, DIF: mesangial strong and diffuse IgG deposits with less intense C3 deposits. G, Pauci-immune proliferative glomerulonephritis: periodic acid–Schiff: epithelial crescents on both glomeruli, on the circumferential upper right portion (arrows) and on the lower circumscription of left hand corner (asterisk). H, Masson trichrome: Bowman space cell proliferation (epithelial crescent, arrow). I, Direct immunofluorescence for C3 with weak deposits on the capillary tuft (traces). No evidence of immune complexes. Color online-figure is available at http://www.jclinrheum.com.

In our series, nephritis was more frequent than previously reported[18]; however, there are multiple case reports of levamisole-cocaine vasculopathy associated with nephropathy,[45-47] making mandatory an active search for kidney disease in these patients. There was great heterogeneity on the histopathologic findings, suggesting an absence of a characteristic pattern and the participation of different physiopathological mechanisms in the development of renal involvement, establishing renal biopsy as a necessity for identification of the type of nephropathy and thus optimal guidance of therapy to lower the chances for ESRD. Although we found variables that were associated with the presence of nephritis (ear necrosis, genital necrosis, anemia, and ANCA positivity), there are no noninvasive biomarkers that predict the type of histological pattern in the biopsy.

Two patients had diffuse alveolar hemorrhage confirmed by fiber-optic bronchoscopy, neither required intubation, and although both patients had renal disease, neither presented with rapidly progressive glomerulonephritis, excluding the use of pulmonary-renal syndrome to describe this type of involvement. Although it is highly unusual, McGrath et al.[18] previously described a similar case, and Carlson et al.[46] reported a patient who presented with a pulmonary-renal syndrome. Regarding hematologic manifestations, we found a lower frequency of leukopenia and neutropenia in comparison with other series (Table 2) and 3 patients with autoimmune hemolytic anemia as has been reported in cases of isolated treatment with levamisole.[48]

In accordance with published data, most of the patients had ANCA positivity (Table 2), with a clear predominance of p-ANCA and anti-MPO. We did not find patients with isolated c-ANCA or anti-PR3 positivity, which also have a very low frequency in other series (Table 2). Although the presence of antibodies directed against nonclassic neutrophil cytoplasmic antigens such as lactoferrin, cathepsin G, and elastase[49,50] has been reported, in 87% of our patients there was positivity against classic antigens

TABLE 4. Pharmacological Treatment on Different Series

	Muñoz-Vahos et al. (Present Study)	McGrath et al.[18]	Chung et al.[19]	Graf et al.[20]	Ullrich et al.[21]	Gross et al.[22]	Khan et al.[23]	Poon et al.[24]
Prednisolone	70	NA	16.7	NA	100	75	75	25
Methylprednisolone	13	NA	33.3	NA	0	0	0	0
Other immunosuppressive drugs	30	NA	0	NA	40	0	25	0
Azathioprine[a]	33	NA	0	NA	0	NA	0	0
Chloroquine[a]	33	NA	0	NA	0	NA	0	0
Methotrexate[a]	22	NA	0	NA	0	NA	100	0
Cyclophosphamide[a]	33	NA	0	NA	100	NA	0	0
Rituximab[a]	11	NA	0	NA	0	NA	0	0
Acetyl salicylic acid	20	NA	0	NA	0	NA	0	0
Anticoagulation	17	NA	0	NA	0	NA	0	0
Colchicine	0	NA	0	NA	0	NA	0	25

Values are presented as percentages.

[a]Percentage of the total of patients who received other immunosuppressive drugs.

NA indicates not available.

(MPO and PR3). The detection of human neutrophil elastase antibodies could differentiate levamisole-cocaine vasculopathy from primary AAV,[51] and Lee et al.[52] have proposed a diagnostic algorithm in patients with suspicion of this disease, which includes the measurement of human neutrophil elastase antibodies. Unfortunately, this assay is not widely available and could not be performed in our patients.

Positivity for APS antibodies was frequent; however, currently it is unknown how long these antibodies remain positive, the associated thrombotic risk, and the necessity of antiaggregation or anticoagulation. Even though microvascular thrombotic compromise is a common manifestation in patients with cutaneous involvement,[29] we found in our series only deep venous thrombosis in the lower extremities of 2 patients, one of whom had a nephrotic syndrome with a proteinuria of 9.6 g/d and LA positivity, which could have favored the thrombotic event; the other patient did not have renal involvement, APS autoantibodies positivity, or other prothrombotic factors besides drug abuse. To our knowledge, these are the first cases of macrovascular thrombosis reported in this vasculopathy.

Antinuclear antibodies and Anti-dsDNA positivity in addition to other clinical and laboratory findings such as hypocomplementemia led to some of our patients fulfilling SLE criteria; thus, it is mandatory to consider levamisole-cocaine vasculopathy as a differential diagnosis when there is a clinical suspicion of SLE. Even though this disease is characterized by multiple autoantibodies positivity, the rheumatoid factor was negative in all our patients.

There are no available treatment guidelines for this entity because of its relative recent description and its low prevalence. The mainstay of treatment is abstinence from consumption and, in most of the patients, the use of glucocorticoids in variable doses according to the severity of the clinical presentation; in some cases, other immunosuppressants were used for their glucocorticoid-sparing effects. The choice of the immunosuppressive agent was guided by the main clinical manifestation in which the treatment has been proven to be effective in other autoimmune diseases.

The long-term impact of therapy due to the follow-up difficulties in these patients is unknown. Because of an elevated risk of infections due to the combination of skin barrier breakdown and the use of immunosuppressive therapy, it is necessary to search alternative treatments that reduce this risk; although there is no clinical experience reported yet, Carmona-Rivera et al.[53] described the in vitro use of muscarinic M3 receptor agonists as a strategy for levamisole-adulterated cocaine-induced NETosis modulation, which should be evaluated in further clinical studies.

This study relies on the information of published reports and patients' charts, and there is a possibility that the entire patient data may not have been available. Because of the infrequency of this disease and social conditions of the patients, it will be difficult to do prospective studies; there are also difficulties to establish cocaine or levamisole doses used and the role of other toxics in the clinical picture. Larger multicenter studies may provide more understanding into the pathogenesis, the spectrum of the disease, and its treatment.

CONCLUSIONS

The clinical characteristics of users of levamisole-adulterated cocaine that develop levamisole-cocaine–induced vasculitis/vasculopathy include painful retiform purpura, with or without central necrosis, and hemorrhagic bullae that affect the ears, face, chest, and limbs. We propose a 4-grade classification that depends on the extension and the severity of the lesions, trying to establish which patients could benefit from immunosuppressive treatment. In addition to multiorganic manifestations, renal involvement is a frequent finding, with a heterogeneous clinical and histological presentation and a high proportion of patients developing ESRD and requiring dialysis.

The main laboratory alterations were acute-phase reactant elevation and the positivity of multiple autoantibodies including ANCAs, LA, aCL, ANAs, and Anti-dsDNA in addition to hypocomplementemia, becoming a differential diagnosis of other autoimmune rheumatic diseases such as SLE, AAV, and APS.

Abstinence from consumption is a fundamental part of treatment, with use of glucocorticoids and other immunosuppressive drugs according to the severity of the manifestations. There is a necessity to develop management guidelines and define the medications of choice, the duration of treatment, and the requirement of cointerventions such as antiaggregation, anticoagulation, and NETosis modulation.

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