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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Cocaine-Induced Vasculitis: Clinical and Immunological Spectrum

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Abstract Levamisole-contaminated cocaine has recently been recognized in North America and Europe, and its use is associated with a variety of clinical and autoimmune abnormalities. The clinical characteristic seems to be the presence of a painful purpuric skin rash that predominantly affects the ear lobes and cheeks, often accompanied by systemic manifestations including fever, malaise, arthralgias, myalgias, and laboratory abnormalities, for example leukopenia, neutropenia, positive ANA, ANCA, and phospholipid antibodies. Most of these manifestations can be seen with the use of either drug, especially levamisole. There is no specific therapy, and discontinuation of its use is followed by improvement. Prednisone and immunosuppressive therapy may be needed at times. Further use of the drug is characterized by recurrence of most of the complaints.

Keywords Vasculitis · Cocaine-induced vasculitis · Levamisole · Cocaine · Midline granulomatous disease · ANCA-associated vasculitis · Clinical · Immunological · Spectrum · Treatment · Musculoskeletal · Diagnosis

Cocaine

Cocaine is a crystalline alkaloid derived from the leaves of the coca plant. It is biologically active with appetite suppressant, central nervous system stimulant, and topical anesthetic properties, and acts as a serotonin–norepinephrine–dopamine reuptake inhibitor [1]. World cocaine consumption is widespread, with the US consuming 50 % of the total, Europe approximately 25 %, and the rest of the world the remaining 25 %. Spain has the highest incidence of cocaine usage (3.0 % of adults), followed by the US (2.8 %), England and Wales (2.4 %), and Canada (2.3 %). Cocaine is the second most popular illegal recreational drug in the US and Europe, after marijuana, and the US is the world's largest consumer with 5.3 million people using the drug in 2008. Cocaine has been ranked both the second most addictive and most harmful of 20 popular recreational drugs [2].

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Clinical Effects

Cocaine is a powerful central nervous system stimulant with rapid onset of action, and whose effects may last up to an hour depending on the route of administration. Its acute use is associated with feelings of increased energy and motor activity, euphoria, reduced need for food and sleep, and enhanced alertness. Anxiety, paranoia, and restlessness may also occur, and, with excessive dosage, tremors, convulsions, and increased body temperature may also develop. Its chronic use, especially when smoked, is associated with multiple side effects including dilated pupils, increases in body temperature, heart rate, and blood pressure, headaches, itching, malaise, flu-like syndrome, sore throat, hemoptysis, alveolar infiltrates, asthma, eosinophilia, abdominal pain, runny nose, lethargy, and also depression and suicidal ideation in heavy users.

Cocaine has also been associated with a great variety of serious systemic and at times life-threatening side effects including dermatologic, pulmonary, cardiovascular, renal, and neurologic, and vasculitis.

Adverse Events

Since 1912, when the first report of cocaine-induced perforation of the palate was described, numerous additional reports have appeared in the literature, some as recently as June 2012 [3, 4•]. Clinical presentation is similar and initially very difficult to distinguish from the upper airways lesions of lymphoma, infection, and, most notably, granulomatosis polyangiitis (Wegener). Imaging investigation often reveals extensive bone-destructive lesions of midline structures, and ulceration of adjacent tissues. Tissue-nasal mucosa, and sinuses, usually reveal a mononuclear inflammatory infiltrate, and very seldom the presence of granulomatous tissue and/or vasculitic involvement. Laboratory investigation is non-specific, but some patients may exhibit elevated acute phase reactants, and ANCA positivity [4•]. Both p-ANCA and c-ANCA, especially p-ANCA, have been described in cocaine-induced midline destruction lesions. ELISA assays for anti-proteinase 3 (Pr3) and myeloperoxidase (MPO) specificities tend to be negative, but anti-elastase specificities have been described in this patient population [5]. A high index of suspicion is needed to establish the diagnosis, and inquiry about the use of cocaine should be always considered in the presence of destructive midline lesions.

Dermatological involvement also occurs in association with cocaine abuse. Palpable purpura, angioedema, urticaria, formication (i.e. tactile hallucinations of insects crawling underneath the skin) bullous diseases, and Stevens–Johnson syndrome have all been described [6, 7]. A clinical characteristic observed is that these manifestations respond to discontinuation of cocaine use, and recur after re-initiation.

Pulmonary clinical and radiological manifestations have also been described in cocaine users. A variety of manifestations might occur including pulmonary edema and hemorrhage, bronchiolitis, asthma, and interstitial pneumonitis [8]. The exact mechanism(s) underlying these manifestations are not clear, and whether cocaine exerts its effects either locally or systemically, the effect of its method of administration (smoking, sniffing, injecting), and its alteration of central nervous system neuroregulation of lung function require further investigation. A recent observation describes the development of cocaine-induced interstitial lung damage in two CYP2C and VKORC1 variant allele carriers. The authors suggest that these polymorphisms contribute to intra-individual variability in cocaine response and toxicity [9].

A variety of cocaine-related cardiovascular manifestations have been described including sudden death, secondary myocardial infarction, aortic dissection, cardiac arrhythmias, ruptured aortic aneurysm, vascular thrombosis, myocarditis, and dilated cardiomyopathy [10]. It is important to keep in mind these complications in cocaine users considering that cocaine intoxication is the most frequent cause of drug-related death reported by medical examiners in the US, and these events are quite often related to the cardiovascular manifestations of the drug. The exact mechanism(s) of how cocaine contributes to these conditions have not been established, however. Clinicians should be highly suspicious of cocaine use in their differential diagnosis of chest pain, especially in younger male individuals.

Renal complications are unusual manifestations seen in cocaine users. Acute and chronic renal insufficiency, glomerulonephritis, glomerulosclerosis, renal infarction, Goodpasture's syndrome, and urogenital tract abnormalities secondary to in-utero exposure to cocaine have all been described [11–13]. The pathophysiology of cocaine-related renal injury is multifactorial and involves renal hemodynamic changes, renal atherogenesis, alterations in glomerular matrix synthesis, and degradation and oxidative stress. Acute severe hyponatremia after cocaine exposure has recently been described. The authors proposed that cocaine, via its effect on the neurotransmitters, stimulates antidiuretic hormone release leading to a syndrome of inappropriate antidiuretic hormone secretion.

Neurological complications have long been recognized in association with cocaine use. Cocaine-induced stroke was first reported in 1977, and since the introduction of "crack" cocaine in the 1980s, there has been a significant rise in the number of reports describing both ischemic and hemorrhagic stroke associated with cocaine use. Pathological examination of selected brain specimens from autopsy cases of cocaine-related cerebrovascular disease has failed to reveal vasculitis [14–17]. These observations suggest that intracranial hemorrhages may occur in the absence of inflammatory vascular abnormalities, and possibly implicate a pharmacodynamic (vasospasm) effect of cocaine. In-vitro studies have shown that cocaine enhances apoptosis of cultured canine cerebral vascular smooth muscle cells in a dose-dependent manner, suggesting it may be of major importance in brain-cerebral vascular toxicity and stroke [18]. Imaging studies may be useful to identify cocaine-induced cerebral vasculitis [19]. The clinical profiles, complications, and disability in cocaine-related ischemic stroke have recently been described [20]. Compared with patients with non-cocaine-related strokes, those with cocaine-related strokes were younger, more likely to be smokers, had higher prevalence of arrhythmias, but less diabetes, similar prevalence of hypertension and lipid profiles, and were less likely to receive statins. Recurrent leukoencephalopathy in a cocaine abuser is a recently recognized complication. Two consecutive episodes of acute leukoencephalopathy, documented by serial MRI, with favorable outcome, have been reported [21].

Systemic necrotizing vasculitis affecting large and small vessels has been described in association with cocaine use. Distinct vasculitic syndromes, for example urticarial vasculitis, Churg–Strauss vasculitis, and granulomatous polyangiitis (Wegener), have been described [22, 23]. The differential diagnosis with other systemic necrotizing vasculitides can be difficult to establish but appropriate inquiry about the use of cocaine will lead to correct diagnosis. It should be noted, however, that none of the cocaine induced vasculitis reported in the English literature described ear necrosis, leukopenia, and neutropenia (Table 1).

Table 1 Cocaine-induced adverse events

Dermatological
- Purpura
- Angioedema
- Urticaria
- Formication
- Bullous disorders
- Stevens–Johnson syndrome
Pulmonary
- Pulmonary edema
- Hemorrhage
- Bronchiolitis
- Asthma
- Interstitial pneumonitis
Cardiovascular
- Sudden death
- Myocardial infarction
- Aortic dissection
- Cardiac arrhythmias
- Rupture aortic aneurysm
- Vascular thrombosis
- Myocarditis
- Dilated cardiomyopathy
Renal
- Acute and chronic renal insufficiency
- Glomerulonephritis and glomerulosclerosis
- Renal infarction
- Goodpasture syndrome
- Urogenital tract abnormalities
- Hyponatremia
Neurological
- Stroke
- Acute leukoencephalopathy
Vasculitis
- Urticarial vasculitis
- Midline granulomatous disease
- Churg–Strauss vasculitis
- Granulomatous polyangiitis

Recent Developments

In April 2008, a clinical reference laboratory in New Mexico notified the New Mexico Department of Health (NMDOH) of a cluster of unexplained agranulocytosis cases confirmed by bone marrow histopathology [24••]. Subsequent investigation of similar cases in British Columbia and Alberta, Canada, and Seattle, Washington, identified common exposure to cocaine contaminated with levamisole in 20 cases [25]. At the time, a review of the literature failed to reveal reports of agranulocytosis associated with cocaine use. This, however, has dramatically changed, and over the past four years, an extraordinary number of reports have appeared in the literature describing a wide variety of clinical and immunological abnormalities associated to the use of levamisole-contaminated cocaine use.

Levamisole

Levamisole is primarily used in veterinary medicine as an antihelmintic drug, but because of its immune system modulatory activity it has been used as an adjuvant in the therapy of specific malignancies, including breast and colon, in the therapy of some inflammatory disorders, for example rheumatoid arthritis, and in pediatric nephrotic syndrome [26, 27]. It has a short half-life (<6 h), and can be detected in the urine within 48 h of last use by gas chromatography–mass spectrometry [28].

Adverse Events

Its clinical use can be associated with multiple side effects including fever, arthralgias, malaise, nausea, vomiting, diarrhea, stomatitis, headaches, flushing, skin rashes such as retiform purpura with or without necrosis and/or hemorrhagic bullae, lividoid pattern, pyoderma gangrenosum, ulcers, lichenoid eruptions, urticaria, angioedema, and much more serious reactions including hemolytic anemia, leukopenia, agranulocytosis, thrombocytopenia, neurological (multifocal inflammatory leukoencephalopathy), and vasculitides [29–31]. These last side effects may have led the FDA to withdraw the drug from the US market.

Levamisole has increasingly been found in street cocaine as an adulterant. The practice of cutting cocaine with levamisole has increased substantially since it was first recognized in early 2000, and by April 2011, according to the Drug Enforcement Administration, over 80 % of cocaine seized in the US contained levamisole. It is not clear why levamisole is added to street cocaine, but it has been speculated that it is added intentionally to potentiate the effects of cocaine [32, 33].

Levamisole-Contaminated Cocaine Use

In early 2008, reports of severe agranulocytosis, subsequently shown to be associated with levamisole-contaminated cocaine use, began to surface. Soon after, several reports including ours began to appear describing a variety of hematological, dermatological, musculoskeletal, and autoimmune manifestations (Table 2).

Hematological Manifestations

In April 2008, a clinical reference laboratory in New Mexico described agranulocytosis cases confirmed by bone marrow histopathology [24••]. The New Mexico Department of Health (NMDOH) subsequently identified cocaine use as a common exposure in a total of 20 cases, which included cases from British Columbia and Alberta, Canada, and Seattle, Washington. Epidemiologic investigation revealed recent or ongoing cocaine use in 14 cases (70 %). Some morphologic features, including circulating plasmacytoid lymphocytes, increased bone marrow plasma cells, and mild megakaryocytic hyperplasia, were associated with the cocaine-exposed group [25].

Table 2 Levamisole-contaminated cocaine use: adverse events

Constitutional
- Fever
- Malaise
Hematological
- Leukopenia
- Agranulocytosis
- Neutropenia
Dermatological
- Purpura: on the helix of ears and cheeks
- Retiform or stellate purpura
- Bullae disorders
- Necrosis
Musculoskeletal
- Arthralgias
- Arthritis
- Myalgias
Vascular
- Leukocytoclastic vasculitis
- Microvascular thrombosis
- Midline granulomatous disease
Miscellaneous
- Hyponatremia
Immunological
- Antinuclear antibodies
- Lupus anticoagulant
- Anticardiolipin antibodies
- P-ANCA and c-ANCA
- Pr3
- MPO

Chai et al. compared the distribution of hematological indices in a population of cocaine users with and without confirmed exposure to levamisole [34]. They reviewed the records of all patients in the Lifespan hospital system that underwent comprehensive toxicologic testing between September 2009 and December 2009 (n=799). Of these, 95 patients were eligible for inclusion (cocaine-positive with a simultaneous complete blood count). Patients were grouped into levamisole-positive (n=47) and negative (n=48) groups. The primary outcome measures were total white cell count (WBC), absolute neutrophil count (ANC), and absolute lymphocyte count (ALC); secondary outcome measures included percentage of neutrophils, lymphocytes, eosinophils, monocytes, and basophils, and identified co-ingestants. The overall incidence of neutropenia was 4.2 % in all cocaine users and 2.1 % in the levamisole-positive group [34]. A striking number of the reported patients with levamisole-associated neutropenia also exhibit associated oropharyngeal complaints, vasculitis, or fever.

So far over 150 cases of neutropenia associated with the use of levamisole-contaminated cocaine have been reported in the US, and the first case in Europe was recently reported [35••, 36••, 37, 38]. A significant proportion of these cases present with systemic febrile illness and infection, or other manifestations, especially dermatological, but this resolves after discontinuation of cocaine use, and without the need to use granulocyte colony stimulating factor. A characteristic, however, is recurrence of neutropenia in up to one-third of cocaine users after re-exposure to levamisole-contaminated cocaine.

The exact mechanism(s) underlying neutropenia remains to be elucidated. Wolford et al., on the basis of the available information on levamisole metabolism in humans, have proposed that reactive metabolite formation is the rate-limiting step in the etiology of agranulocytosis associated with levamisole, in a manner similar to other drugs (e.g., propylthiouracil, methimazole, captopril, etc.) associated with blood dyscrasias [39].

Dermatological Manifestations

A variety of skin manifestations, including purpuric macules and papules on the helix of the ear or the cheeks, retiform or stellate purpura on the trunk and extremities, bullae formation, and frank extensive necrosis and crusting eschars are the second most common manifestations observed after exposure to levamisole-contaminated cocaine. Histopathological examination reveals leukocytoclastic and necrotizing

vasculitis in a significant proportion of cases. However, thrombogenic vasculopathy with no inflammatory infiltrate has also been described. The term LIVEN, levamisole-induced vasculopathy, has recently been introduced. A novel histopathologic finding described in one case was the presence of extensive interstitial and perivascular neovascularization [40–42].

Musculoskeletal Manifestations

Myalgias, arthralgias and frank arthritis may also be seen. At times, a symmetric polyarthritis of large and small joints that mimic rheumatoid arthritis (RA) can be present [36••]. We have observed several patients with RA-like presentation, but with negative rheumatoid factor and anti-CCP antibodies. Arthralgias and arthritis can be present concomitant to other clinical and serologic manifestations, especially skin and anti-phospholipid and ANCAs—mostly in a perinuclear pattern. Joint manifestations respond well to NSAIDs and/or low-dose prednisone therapy.

Vascular Manifestations

Beginning 2009, we and others began to recognize a cluster of patients presenting with diffuse painful purpuric and at times necrotic skin rash, over the extremities, trunk, back, with preferential involvement of ear lobes and cheeks [36••, 43–45]. In our initial report, we described four patients with this type of skin involvement, but we have since had the opportunity of examining four other patients with similar characteristics. To date, there are more than 25 reports in the literature and the number continues to increase. Vascular involvement can be demonstrated at the microscopic level by a mixed pattern of leukocytoclastic vasculitis and microvascular thrombosis. This type of histopathology finding seems to be characteristic of levamisole-induced vasculitis. These vascular lesions may resolve spontaneously after discontinuation of levamisole-contaminated cocaine use, or after initiation of glucocorticoid therapy. Vascular lesions, however, may recur after re-initiation of the drug.

Inflammatory vascular disease may co-exist with other systemic clinical and serological manifestations, including arthritis, fever, leukopenia, neutropenia, positive ANA, p-ANCA and c-ANCA, PR3 and MPO [46•, 47, 48].

The exact pathogenesis of levamisole-contaminated cocaine use is not known. Both levamisole and cocaine can induced or unmask latent immunological abnormalities with the formation of auto-antibodies, including ANA, ANCA, anti-phospholipid, and immune complex deposition, which adhere to the surface of blood vessels, degranulate, and release toxic oxygen metabolites and eventually leading to vascular injury.

Miscellaneous Manifestations

Hyponatremia has been described in three patients presenting to an emergency department. Despite extensive evaluation, the cause of the hyponatremia was not elucidated but resolved during hospitalization. Levamisole was detected in all three patients [49].

Immunological Manifestations

A variety of autoantibodies can occur during the course of cocaine use with or without levamisole contamination. Higher frequencies of autoantibodies occur after use of levamisole-contaminated cocaine. Between 15 to 80 % of patients presenting with levamisole-contaminated cocaine-induced vasculopathy exhibit circulating lupus anticoagulant, anticardiolipin antibodies, ANAs, p-ANCA, c-ANCA, PR3, and MPO antibodies (Table 2).

Diagnosis

A high index of suspicion is needed for a definite diagnosis. Prompt urine toxicology testing using gas chromatography–mass spectrometry is essential, because of the short-elimination half-life of levamisole, and only a small amount of the parent drug (<5 %) is detected in urine. Cocaine metabolites are detected up to 3.4 days on average after last use. Discordance between the patterns of ANCA observed on immunofluorescence and the specific antigenic targets provide a clue for diagnosis of cocaine-induced vasculitis. Elevated levels of antibodies to human neutrophil elastase can assist in the detection of cocaine-related vasculopathy.

Treatment

There is no specific therapy, but cessation of levamisole-contaminated cocaine use leads to improvement and eventually remission of all clinical and serological manifestations. Clinical manifestations usually improve in a matter of days, and complete disappearance occurs after a few weeks. Serological manifestations usually last longer, but also become negative after several weeks to a few months. Prednisone and other immunosuppressive agents, especially methotrexate, may be used in patients with extensive vasculitic involvement. Prednisone doses of 20–40 mg daily and tapered down over 3 to 4 weeks are highly effective [36••].

Neutropenia also improves after discontinuation of levamisole-contaminated cocaine use, and there is no need for the use of granulocyte colony-stimulating factor.

Drug counseling is recommended, but in our experience most patients continue to use the drug and recurrence of clinical and serological manifestations is a common occurrence.

Conclusions

Levamisole-contaminated cocaine use is an emerging public health challenge [50••]. Its use is increasingly recognized to be associated with a variety of clinical and laboratory manifestations that resemble autoimmune disorders, especially vasculitis; and should be considered in the differential diagnosis of systemic necrotizing vasculitides. A high index of suspicion is needed, and to confirm the diagnosis, a prompt urine toxicology testing to detect levamisole in the urine is essential. In most cases, cessation of the drug use leads to improvement of all clinical and serological manifestations.

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