Review Article

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Immune-mediated clinical manifestations associated with cocaine-levamisole use- A literature review

We know the previously described relationship between the cocaine consumption and the development of clinical inmuno-meditated conditions, so frequently mimicking ANCA-vasculitides. We made a detailed revision of the current knowledge about this topic, also pointing out the changes in the clinical and laboratory findings that seems to occur in the last decades, and their suspected relation with the broad use of levamisole as cutting agent. Finally we summarised the management options described in the literature.

Keywords: cocaine ● levamisole ● vasculitis ● ANCA ● biological therapies

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Introduction

Cocaine has been widely used in medicine as a local anaesthetic due to its powerful vasoconstrictor action. From a neuropsychiatric perspective, it has a powerful psychostimulant effect that mainly results from dopamine reuptake inhibition in the synaptic cleft; this effect has led to cocaine becoming a widely consumed illicit drug. The recreational use of cocaine accounts for 0.4% of the general population between ages 15 and 64 [1], it is estimated that within this age group around 13 million Europeans have used cocaine at least once [2]. Data obtained in 2008 in USA estimated the number of consumers at over 36.5 million [3]. The most common route of administration is inhalation through the nose, and its use is frequent in a polydrug context.

Levamisole is fundamentally used as an anthelmintic in veterinary practice. Due to its immunomodulatory properties, it has been used to treat Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Behçet's disease, lichen planus, Crohn's disease, vitiligo, etc. [4]. It has also been used as adjuvant chemotherapy for breast cancer, colon cancer and melanoma [4]. It is an imidazole derivative that acts as a nicotinic antagonist, induces release of glutamate, and intensifies the dopaminergic and psychostimulant effect of cocaine. It is estimated that levamisole can be found as an adulterant in 70-90% of consumed cocaine with concentrations of 1.5 to 10% [5,6]. Its physical and chemical characteristics make it an ideal cutting agent, macroscopically similar to cocaine, with a short half-life (roughly 5.6 hours) and complex detection, its quantification only can be carried out by specialized laboratories [7].

A thorough review of available knowledge on the different clinical processes associated with consumption of both substances was performed, especially of those processes posing a challenge to differential diagnosis in relation to autoimmune conditions. Described clinical pictures associated with cocaine use are conditioned by underlying vascular trauma; some of these with vasculitic features and others of difficult differential diagnosis regarding the former. Clinics of leukocytoclastic vasculitis, agranulocytosis, glomerulonephritis, leukoencephalopathy and other manifestations have been described as associated with the use of levamisole from the 70's [8-10]. The frequent appearance of autoantibodies, especially ANCAs, in association with consumption of both substances is remarkable [4,11,12].

Pathogenesis

Establishing a specific etiopathogenic correlation between the use of each of these substances and their subsequent clinical manifestations is difficult in a substantial number of studies, particularly the most recent ones, due to the increased frequency of levamisole presence as an adulterant.

A substantial part of organ damage associated with the use of cocaine/levamisole, and mostly forms of vascular affectation and systemic processes, is mediated by induced autoimmune phenomena. This is demonstrated by the frequent presence of ANCA, characteristically with high titers and mixed patterns of immunofluorescence (p-ANCA and c-ANCA; p-ANCA positivity being the most frequent) directed against various antigenic specificities (atypical specificities such as elastase or lactoferrin being the usual as compared to the classical MPO and PR3) [4,13,14]. On one hand, ANCA titers typically high and mixed patterns, and on the other hand, the atypical ANCA antigens are two key elements for differential diagnosis in these processes. Cocaine use associated with clinics that are very similar to 'classic' granulomatosis with polyangiitis (GPA) with c-ANCA positivity and anti-PR3 specificity is something that cannot be ignored [4,15].

Some authors indicate that data published in past decades in connection with development of vasculitis induced by cocaine consumption are strikingly low when compared to current data. Furthermore, emphasis is placed on the fact that the relatively few described cases presented autoimmunity profiles that were significantly different from those observed in most recently described cases with anti-PR3 predominance and very scarce presence of anti-MPO. For this reason, it is hypothesized that the frequent presence of levamisole used as an adulterant plays a role in the apparent increase in the number of cases, as well as in their clinical and serological profiles [11,16,17]. During the second decade of this century, there has been a striking emergence of clinical profiles with agranulocytosis, cutaneous vasculitis, and other non-habitual manifestations in cocaine consumers. This emergence seems to be clearly linked to levamisole being added as a cutting agent, which has increased in the US from under 10% in 2007 to over 70% in 2009 [18].

The mechanism underlying ANCA development and/or endowing a pathogenic potential to these is unknown. Antigens which ANCA classically direct against (MPO and PR3) are located inside the neutrophil cytoplasmic granules, and therefore, have limited exposure to the immune system. In recent years, Neutrophil Extracellular Traps (NETs) have become increasingly significant, not only in the pathogenesis of ANCA vasculitis, but also in other autoimmune processes (SLE, psoriasis, RA, etc.) [19,20]. In apoptotic processes, activated neutrophils release NETs (structures containing DNAds, histones, and granules that can harbor MPO, PR3, elastase, cathepsin G, lactoferrin and other proteins) [21]. It is been suggested that the NETosis process (NET release) could have a bidirectional relationship with ANCA presence, therefore it could induce ANCA development and formation, and in turn it could be induced by ANCA presence, thereby establishing a positive feedback loop. Constituent components of these structures (especially MPO and PR3) are directly associated with autoimmune phenomena induction [21,22]. Complementarily, the NETosis process can be induced by ANCAs, IgGs, immune complexes, etc. [22].

There is documentation substantiating NET presence revealed in kidney biopsies of patients with ANCA vasculitis, and afterwards, its presence in skin lesions has also been documented [23,24]. Patients with ANCA vasculitis have higher circulating levels of NETs, although a potential link between its presence and concentration and the development of the disease is uncertain [25,26]. NETs have been involved in diverse forms of inflammatory phenomena, can induce direct endothelial damage, activate the alternative pathway of the complement system, and have a prothrombotic influence. It has been theorized that they can have a significant structural role in blood clot formation and coagulation cascade activation [6].

Both cocaine and levamisole seem to be able to induce release and exposure of elastase and other NET constituent structures. There is also documentation substantiating that IgGs of patients with vasculitis induced by cocaine/levamisole enhance NETosis process and induce release of elastase and other constituent components [4,27]. Finally, presence of antibodies directed against NETs, with or without vasculitic manifestations, has been observed in patients using adulterated cocaine. Some data would sustain the existence of genetic factors favoring or promoting ANCA formation in cocaine consumers [14,28]. Similar models of ANCA vasculitis induced after toxic exposure and key participation of NETs have been detected after exposure to propylthiouracil [29].

Pathogenic studies performed in a specific clinical context [14] of Cocaine-Induced Midline Destructive Lesions (CIMDL) point to the importance of local vasospasm, local trauma caused by cocaine crystals, ischemia/

necrosis, superinfections and, very interestingly, immunological and induced apoptotic phenomena in the development of these lesions. Taken together, these factors confer and define the individual risk of a patient. Some studies emphasize the importance of apoptotic phenomena in these forms of vasculitis [30]. As they are not found in healthy patients' nasal biopsies or observed in GPA patients, apoptosis presence seems to be a typical histologic feature in ANCA vasculitis induced by cocaine. The etiopathogenic importance that NETosis could have in the context of apoptosis and induction of autoimmunity must be noted.

Other pathways potentially involved in systemic autoimmune condition and/or vascular damage development have been found in connection with cocaine/levamisole use. First publications observing the existence of levamisole-induced vasculitis date back to 1978 [31]. There are some published case series of children with vasculitis who had been treated with levamisole due to nephrotic syndrome from the 90's [9]. These publications already describe the main clinical characteristics with presence of skin lesions typically located in ears, cheeks, etc., and presence of various autoantibodies (ANCA, anti-DNA, lupus anticoagulant). Levamisole can induce alterations in mechanisms of auto-tolerance, and genetic predisposition plays a role here [32-34]. Clinical profiles of persistent autoimmune condition induced by levamisole are also described [32]. The case of an adult treated with levamisole due to vitiligo and subsequently developing extensive skin necrosis, coagulopathy, thrombocytopenia and intracranial hemorrhage, with p-ANCA and Lupus Anticoagulant (LA) positivity is described; organ affectation persisted for more than 4 years after the consumption of the drug.

A significant proportion of patients treated with levamisole present agranulocytosis. The mechanism involved in agranulocytosis is unknown, it appears in up to 20% of treated patients, and there seems to be a degree of special susceptibility in individuals who are HLA-B27 (+) [35]. In some case series, patients have developed neutropenia/agranulocytosis in up to 75% of cases [36-38]. Levamisole use has also been associated with the appearance of liver and gastrointestinal toxicity [6,15]. The presence of neutropenia/agranulocytosis is key information for differential diagnosis of ANCA vasculitis induced by cocaine-levamisole as compared to other toxic substances [15].

A small case series of four cases describes positivity of anti-C1q in 3/4 cases of vasculitis induced by cocaine-levamisole (frequency significantly higher than the one observed in context of other forms of vasculitis in which they were determined); overall 5.3%, including ANCA-vasculitis (13 cases), PAN (4 cases), Takayasu disease (2 cases). Among positive cases, levels were significantly higher in vasculitis induced by cocaine/levamisole as compared to other forms of vasculitis (51.0 ± 25.3 vs. 10.4 ± 7.1 IU, p = 0.04). Based on these data and knowing the role that C1q has in processes of clearance and elimination of apoptotic debris, there is speculation that these antibodies have a possible pathogenic role in the development of these forms of vasculitis and its possible use in diagnostic tests for these patients.

Finally, it is important not to forget the importance of ischemic damage, both local and systemic, that is induced by cocaine and due to vasospasm, endothelial dysfunction and thrombophilia; these effects are mediated, among others, by platelet factor 4 increase, thromboglobulin, P-selectin and endothelin 1, and nitric oxide decrease [39].

Clinical profile

Cutaneous and mucosal affectation

Most vascular clinical profiles have only cutaneous manifestations (>90%), although in some cases there can be coexistence with visceral damage: kidney, lung, cardiac, liver, and neurological. Systemic manifestations can appear (72%) with fever, weight loss and night sweats, as well as joint involvement (arthralgias/arthritis 31-83%), even with peripheral symmetric pattern, mimicking RA [11,40,41].

Cutaneous damage is characterized by presence of purpuric macules and plaques of reticular distribution ('retiform' pattern) with an active edge and necrotic center [42], painful hemorrhagic vesicles and bullae. They can appear in any location, but mostly in pinna, cheeks, nose and lower limbs [13,43,44]. They can evolve towards necrotic ulcers and have a high risk of infection. Involvement of the pinna is described as typical and characteristic [6], but the most frequent location of lesions is in lower limbs. In the Pearson et al. study, the following frequency of affectation is indicated in descending order: lower limbs 84%, ears 73%, upper limbs 62%, face 47%, torso 49%, and nose 38% [41]. The clinical pattern of cutaneous vasculitis described is habitually attributed to levamisole exposure [8]. The frequency of this clinical picture seems to have increased in recent years, which is associated with frequent use of levamisole as an adulterant. Although consumption figures seem to be higher among men, cutaneous vasculitis is more frequent among women [8,45]. The serological profile of these patients is very

varied, with frequent presence of ANCA (p-ANCA and c-ANCA), anti-DNA, anti-RNP, etc. Approximately, half of these patients had accompanying neutropenia [8]. Although it is true that the described clinical picture is characteristically attributed to levamisole exposure, the typical triad for some authors (cutaneous vasculitis, neutropenia and ANCA positivity) [45,46], it could be induced by the vasoconstrictor effect attributable to cocaine and to autoimmune phenomena that are potentially due to exposure to both substances [33].

A specific pattern of mucosal involvement is characterized by the presence of Cocaine-Induced Midline Destructive Lesions (CIMDL) that could be considered as a differentiated and well-defined clinical entity. It is characterized by destructive mucosal lesions of midline facial areas that can affect underlying cartilaginous and bone tissue and provoke widespread destruction. It affects up to 4.8% of consumers who use cocaine through nostril inhalation (this frequency corresponds to the mildest clinical manifestation consisting in nasal septum perforation) [14], with potential involvement of hard and soft palates, nasal turbinate, pharyngeal area, etc. [47]. Differential diagnosis essentially consists of ORL area, lymphomas, infectious diseases (TB, syphilis, fungal diseases, Leishmania), sarcoidosis and autoimmune systemic processes (essentially ANCA vasculitis). Differential diagnosis between CIMDL and GPA may be complex. Based on comparative analysis of one case series, the following differential clinical characteristics can be highlighted [48] (Table 1).

MRI could be the most useful imaging technique to depict midline destructive lesions. It is worth noting that this study observes that nasal perforation has a PPV 88.9% for CIMDL final diagnosis. Damage of a second structure of the midline revealed itself as a highly discriminative finding (75% in CIMDL vs. none in GPA), while isolated nasal affectation, in the absence of other data on the disease, is extremely rare in GPA [14].

Kidney involvement

Kidney damage rarely occurs, but it has been consistently documented. This work revises the McGrath et al. [11] and Neel et al. [18] studies. In the case series published by McGrath et al., eight out of 30 reviewed patients had kidney alteration characterized by presence of proteinuria (non-quantified, determined with test strip), hematuria, erythrocyte dysmorphia and abnormalities in sediment. Two out of these eight patients developed severe kidney damage with a marked deterioration of renal function (Cr 7.7 mg/dl and 5.6 mg/dl) combined with frank proteinuria and hematuria. A renal biopsy was performed on one of these patients, revealing pauci-immune focal proliferative and necrotizing glomerulonephritis. None of these cases required renal replacement therapy. In both cases, immunosuppressive treatment was initiated with overall kidney function improvement, but persistent and significant chronic functional deterioration with glomerular filtration around 30 ml/min. From a serological perspective, it should be mentioned that all eight patients were anti-MPO positive, three out of the eight patients were anti-PR3 positive (note that the two patients with highest level of renal affectation presented anti-PR3 and anti-MPO positivity). The patient who was biopsied also presented a decrease in C3 levels, positivity for anti-DNAds, and Lupus Anticoagulant (LA).

In the Neel et al. study case series, 18 published cases with histologically documented glomerulonephritis attributed to cocaine/levamisole were compiled, being the pauci-immune necrotizing extracapillary glomerulonephritis the most frequent pattern (8/18). In 17 cases renal involvement was the initial manifestation or was part of the initial clinical spectrum. Cutaneous lesions occurred in 15 cases. Out of the 17 patients underwent ANCA tests, 16 cases were positive anti-MPO and 8 cases were anti-PR3. To note AL determination was only performed in 8 cases (6 were positive).

Table 1. Differential clinical characteristics between Cocaine-Induced Midline Destructive Lesions (CIMDL) and granulomatosis with polyangiitis (GPA).

CIMDL	GPA
• Nasal obstruction, epistaxis, severe facial pain • Diffuse necrotizing ulcerative lesions, nasal septum and inferior turbinate destruction • Hard and soft palate perforation • Possibility of widespread periorbital affectation (orbital pseudotumor) • Centrifugal spreading of affectation • Absence of systemic symptoms	• Milder nasal destruction, infrequent nasal perforation, palate or turbinate not affected • More diffuse upper airways affectation pattern, without clear preponderance for midline or centrifugal distribution • Systemic symptomatology • Frequent affectation in other systems/organs: lower airways, ear, kidney, PNS …
UAW: upper airway, PNS: peripheral nervous system	

Pulmonary affectation

Pulmonary involvement is considered to be infrequent. Reported data essentially refer to alveolar hemorrhage development. In the McGrath, et al. study [11] cohort, three out of 30 patients developed alveolar hemorrhage, and only one of them presented alterations in urine sediment, so the pulmonary renal syndrome total development remains undocumented. The Carlson et al. study [49] presented the case of a female patient with hepatitis C who initially developed a typical cutaneous profile in combination with renal damage (Cr mild deterioration, hematuria, not quantified proteinuria and alterations in sediment). Months later, this patient developed a frank renal pulmonary clinical picture with marked deterioration of renal function (Cr 7.31 mg/dl), hematuria, proteinuria, and alterations in sediment, to which a frank alveolar hemorrhage was added. Strikingly, the 4 reported cases are positive for anti-MPO, and only one of them presents anti-PR3. Based on available data, we can presume that lungs are also target organs in processes of autoimmune condition induced by cocaine/levamisole. Nevertheless, evidence is significantly less robust than in other areas, and it is more likely that local effects play a key role here.

Neurological involvement

Regarding the Central Nervous System (CNS), cocaine related damage (beyond the stupefying effects) is primarily connected with its vasospastic effect and subsequent occurrence of ischemic events, hemorrhagic events, clinical pictures of reversible cerebral vasoconstriction (of complex differential diagnosis with primary vasculitis of the CNS at times), etc.

On the other hand, Progressive Multifocal Leukoencephalopathy (PML) development has been documented in association with both cocaine and levamisole consume. Cocaine-induced PML has variable clinical characteristics such as inattention, forgetfulness, changes in personality, dementia, even sensory and motor deficits, decreased levels of consciousness, spasticity or bradykinetic rigid syndromes [50]. MRI scans typically reveal white-matter abnormalities involving both hemispheres, predominantly ventricular in FLAIR and T2 sequences, the U fibers appear preserved, there is absence of restriction of diffusion or enhancement with gadolinium, increased lactate and decreased N-acetylaspartate in spectroscopy [51]. Brainstem and cerebellum are areas that are normally not affected. The clinical evolution can be variable, and it can range both from rapid progression to death [52] or recovery with subsequent recurrence in some cases [50,51].

Regarding levamisole-induced lesions, there is a case series of patients with PML associated with levamisole use in different clinical contexts. Correlation between dose and observed damage was not observed, therefore it is suggested that this is somewhat idiosyncratic. Time of exposure until onset of clinical manifestations was variable, even with the first dose. Normally, there was improvement after stopping exposure. In parallel, changes observed with MRI appeared much later, over nine months. In this context, and considering the evolution, this seems to be a reversible process taking place after suspending the use of the drug [10].

Diagnosis

Considering inflammatory vascular process and/or autoimmune systemic process as secondary manifestations to cocaine/levamisole use is diagnosis of exclusion. It starts based on clinical suspicion, usually with acute onset of purpuric lesions of retiform distribution with central necrosis and particular predilection for pinna, combined with systemic manifestations (fever, asthenia) and arthralgias. In approximately 60% of cases there is coexistence of hematologic alterations and ANCA positivity at medium-high titers in 95-100% of patients [4,53] in some case series, this being the serological finding of highest value.

The most common pattern of immunofluorescence is p-ANCA, in some case series reaching 88-100% of patients with specificity for MPO in 66-100% [11,41]. A characteristic feature is the presence of mixed patterns of immunofluorescence with coexistence of p-ANCA and c-ANCA, in such a way that in the McGrath et al. study case series, 50% were also anti-PR3; in the Gulati et al. revision with 66 patients with vasculitis induced by cocaine/levamisole, 66% were PR3 positive compared to 56% MPO [54]; and in the Neel et al. study case series with 17 patients where ANCAs were determined, 16 patients were positive for anti-MPO and practically 50% had positivity for PR3 [18]. ANCA positivity is frequent and characteristic with atypical specificities such as anti-elastase (protein that shares epitopes with PR and can give a false positive anti-PR3), lactoferrin and cathepsin G.

Going deep into ANCA significance and value in this context, in some case series of patients with CIMDL, PR3-ANCA positivity reaches 50% [16]; different studies yield results suggesting that a significant percentage of anti-PR3 would direct against antigens different from those to which anti-PR3 direct in GPA context [55]. The Trimarchi et al. study [48] notes that, overall, determination of ANCA in isolation conferred

poor capacity to discriminate in differential diagnosis between GPA and CIMDL, although a more detailed analysis of antigenic specificities was much more limited in GPA. In fact, none of the GPA patients analyzed in the case series showed anti-elastase positivity. Other studies, document ANCA positivity in practically 100% [16] with p-ANCA pattern and fundamentally directed against elastase. Approximately half of patients present PR3-ANCA positivity. It could be said that in CIMDL, ANCA positivity is directed against different specificities that are frequently mixed, atypical and at high titers [55].

It is not infrequent to find titers, frequently low-medium, of ANA, anti-DNAds and antiphospholipid [6,11,56].

From an analytical perspective, attention should be drawn to neutropenia (associated to levamisole exposure). Elevation of acute phase reactants and hypocomplementemia, documented in some cases would be rather nonspecific.

In histological terms, leukocytoclastic vasculitis, thrombotic vasculopathy and mixed phenomena can be found. At cutaneous level, there is typically vascular affectation in the upper and lower layers of the dermis, with an angiocentric mixed infiltrate in which there is usually predominance of neutrophils, occasionally with significant eosinophilic populations. Infiltration of vessel wall, leukocytoclasis, fibrinoid necrosis and vascular extravasation appear [15,57]. Vascular obstruction with fibrinoid trombii and dermal and epidermal secondary necrosis without vasculitis may occur [7,58].

In the CIMDL cases, histologic differentiation vs. GPA is usually complex due to findings that are common in both processes. There are no findings that are clearly specific to CIMDL, although for some authors the assessment of apoptotic phenomena could be very useful for differential diagnosis [30]. Therefore, a histologically confirmed diagnosis is only possible if specific data for GPA are found [14]. There is the additional fact that histological yield of nasal or ORL samples in patients diagnosed with GPA is around 50% [14,59].

Treatment

Stopping exposure is the first and fundamental step, combined with the adoption of general supportive measures and prevention of complications.

In the CIMDL specific context [14], some authors consider immunosuppressive therapy not to be suitable to solve it, except for those cases of persistent affectation. For these cases, if abstention is really confirmed, differential diagnosis should be reviewed with caution.

Immunosuppressant use has been reported in cases with significant organ affectation. Glucocorticoids are only for individuals not improving with general supportive measures or for those individuals presenting systemic affectation. This way, for example, treatment for levamisole-induced vasculitis is fundamentally conditioned by clinical presentation. In the Pearson et al. study case series, with cutaneous manifestations without evidence of severe organ damage in most of the cases, 60% of patients received steroids while 40% were treated with supportive measures according to their needs. The study's authors noted that data did not firmly sustain the fact that GC use improved the disease course, but it was justified for particularly aggressive forms [41]. Similarly, in the Gulati et al. study case series, also consisting of cases of predominant cutaneous affectation, 43% received immunosuppressive therapy while it was not used in 57% of cases, the resolution of clinical manifestations was primarily associated with abstention more than with specific treatment. In this case series, a continued substance consumption was associated with a recurrence rate of 44% [54].

In those cases of visceral involvement with risk for organ failure, immunosuppressive therapy must be considered as a key element in treatment. There are available data on the treatment in 20 cases out of a review of 22 published cases (Neel et al. study's 18 cases already mentioned and others recently published) describing renal affectation due to cocaine/levamisole use [6]: 13 glucocorticoids and cyclophosphamide, 3 glucocorticoids and rituximab, 3 glucocorticoids in monotherapy, and 1 cyclophosphamide in monotherapy. Four out of twenty cases required plasmapheresis. With respect to the evolution, in the medium and long term, 15 patients experienced improvement, or at least renal function stabilization, while 6 required renal replacement therapy. Cr mean concentration at initial clinical manifestation was significantly higher among patients who eventually required renal replacement therapy (11.05 mg/dl vs. 3.25 mg/dl). Treatment schemes used in patients developing alveolar hemorrhage are practically superimposable to those described for renal involvement, and in some way they are similar to schemes recommended in a primary vasculitis context according to the existing organ affectation.

Prognosis

Prognosis is generally favorable. It should be noted that most of patients present a non-aggressive course, with predominance of cutaneous affectation. Nevertheless, there is a major increase of morbidity and mortality,

as well as chronic and irreversible damage with clinical pictures of extensive cutaneous involvement and/or visceral involvement.

Prognosis in the medium to long term is fundamentally conditioned by stopping substance use. Cutaneous lesions tend to initiate regression after 2-3 weeks and neutropenia in 5-10 days, but serological alterations are usually much more persistent, over 14 months [47,60]. As seen above, for those cases with significant organ damage, there is a non-negligible chronic sequelae risk which justifies treatment schemes that are aggressive in their initial form, similar to those used in primary forms of ANCA vasculitis, combined with strict follow-up and monitoring.

Conclusion

Emergent literature indicates a higher frequency in the occurrence of immune-mediated adverse effects due to cocaine use, although for obvious reasons real incidence and prevalence cannot be known with absolute certainty since the consumer population size is not known. Clinical and analytical characteristics of signs and symptoms related to cocaine use also seem to be changing over recent decades, which are attributed to the more and more frequent use of levamisole as a cutting agent. Levamisole in turn is also the cause of some relatively specific manifestations.

Final diagnosis is considered to be diagnosis of exclusion, therefore evidence on consumption is of key importance in those cases that are clinically suggestive. Regarding complementary tests, ANCA determination and frequent positivity at higher titers, mixed patterns of immunofluorescence and positivity against atypical specificities are highly indicative data.

The vast majority of cases present cutaneous and mucosal manifestations that habitually respond favorably after stopping substance use. However, it should be taken into account that there is a possibility of signs and symptoms that are potentially serious and similar in presentation, progression, prognosis, treatment and evolution to primary ANCA-vasculitis.

References

1. https://www.unodc.org/doc/wdr2016/WORLD_DRUG_ REPORT_2016_web.pdf
2. European Commission. Young people and drugs among 15–24 year-olds. *Flash Eurobarometer.* (2008).
3. SAMHSA, Office of Applied Studies. National Survey on Drug Use and Health. Illicit Drug Use Tables. (2007)
4. Marquez J, Aguirre L, Munoz C *et al.* Cocaine-Levamisole Induced Vasculitis/Vasculopathy Syndrome. *Curr. Rheumatol. Rep.* 19(6), 36 (2017).
5. Chung C, Tumeh PC, Birnbaum R *et al.* Characteristic purpura of the ears, vasculitis, and neutropenia– a potential public health epidemic associated with levamisole adulterated cocaine. *J. Am. Acad. Dermatol.* 65(4), 722–725 (2011).
6. Jina Q, Kantb S, Alhariric J *et al.* Levamisole adulterated cocaine associated ANCA vasculitis: review of literature and update on pathogenesis. *J. Community Hosp. Intern. Med. Perspect.* 8(6), 339–344 (2018).
7. Tran H, Tan D, Marnejon TP. Cutaneous vasculopathy associated with levamisole-adulterated cocaine. *Clin. Med. Res.* 11(1), 26–30 (2013).
8. Buchanan JA, Lavonas EJ. Agranulocytosis and other consequences due to use of illicit cocaine contaminated with levamisole. *Curr. Opin. Hematol.* 19(1), 27–31 (2012).
9. Rongioletti F, Ghio L, Ginevri F *et al.* Purpura of the ears: a distinctive vasculopathy with circulating autoantibodies complicating long-term treatment with levamisole in children. *Br. J. Dermatol.* 140(5), 948–951 (1999).
10. Wu V, Huang JW, Lien HC *et al.* Levamisole-induced multifocal inflammatory leukoencephalopathy: clinical characteristics, outcome, and impact of treatment in 31 patients. *Medicine.* 85(4), 203–213 (2006).
11. McGrath MM, Isakova T, Rennke HG *et al.* Contaminated cocaine and antineutrophil cytoplasmic antibody-associated disease. *Clin. J. Am. Soc. Nephrol.* 6(12), 2799–2805 (2011).
12. Veronese FV, Dode RS, Friderichs M *et al.* Cocaine/levamisole-induced systemic vasculitis with retiform purpura and pauci-immune glomerulonephritis. *Braz. J. Med. Biol. Res.* 49(5), e5244 (2016).
13. Graf J. Rheumatic manifestations of cocaine use. *Curr. Opin. Rheumatol.* 25(1), 50–55 (2013).
14. Trimarchi M, Bussi M, Sinico RA *et al.* Cocaine induce midline destructive lesions-An autoimmune disease? *Autoimmun. Rev.* 12(4), 496–500 (2013).
15. Nolan AL, Jen KY. Pathologic manifestations of levamisole adulterated cocaine exposure. *Diagn. Pathol.* 10, 48 (2015).
16. Wiesner O, Russell KA, Lee AS *et al.* Antineutrophil cytoplasmic antibodies reacting with human neutrophil elastase as a diagnostic marker for cocaineinduced midline destructive lesions but not autoimmune vasculitis. *Arthritis. Rheum.* 50(9), 2954–2965 (2004).
17. Neynaber S, Mistry-Burchardi N, Rust C *et al.* PR3-ANCApositive necrotizing multi-organ vasculitis

following cocaine abuse. *Acta. Derm. Venereol.* 88(6), 594–596 (2008).

18. Néel A, Agard C, Hamidou M. Vasculitides induced by cocaine and/or levamisole. *Joint. Bone. Spine.* 85(1), 9–14 (2018).
19. English JCI. Granulomatous disorders of adult skin, an issue of dermatologic clinics. Philadelphia (PA): Elsevier Health Sciences. (2015).
20. Al-Hussain T, Hussein MH, Conca W *et al.* Pathophysiology of ANCA-associated vasculitis. *Adv. Anat. Pathol.* 24(4), 226 (2017).
21. Sangaletti S, Tripodo C, Chiodoni C *et al.* Neutrophil extracellular traps mediate transfer of cytoplasmic neutrophil antigens to myeloid dendritic cells toward ANCA induction and associated autoimmunity. *Blood.* 120(15), 3007–3018 (2012).
22. Söderberg D, Segelmark M. Neutrophil extracelular traps in vasculitis, friend or foe? *Curr. Opin. Rheumatol.* 30(1), 16–23 (2018).
23. Kessenbrock K, Krumbholz M, Schonermarck U *et al.* Netting neutrophils in autoimmune small-vessel vasculitis. *Nat. Medicine.* 15(6), 623–625 (2009).
24. Abreu-Velez AM, Smith JG, Howard MS. Presence of neutrophil extracellular traps and antineutrophil cytoplasmic antibodies associated with vasculitides. *N. Am. J. Med. Sci.* 1(6), 309–313 (2009).
25. Wang H, Sha L, Ma T *et al.* Circulating level of neutrophil extracellular traps is not a useful biomarker for assessing disease activity in antineutrophil cytoplasmic antibody-associated vasculitis: e0148197. *PLoS ONE.* 11(2), e0148197 (2016).
26. Söderberg D, Segelmark M. Neutrophil extracellular traps in ANCA-associated vasculitis. *Front. Immunol.* 7(UNSP 256), 256 (2016).
27. Lood C, Hughes GC. Neutrophil extracellular traps as a potential source of autoantigen in cocaine-associated autoimmunity. *Rheumatology (Oxford).* (2016).
28. Carmona-Rivera C, Purmalek MM, Moore E *et al.* A role for muscarinic receptors in neutrophil extracellular trap formation and levamisole-induced autoimmunity. *JCI. Insight.* 2(3) (2017).
29. Nakazawa D, Tomaru U, Suzuki A *et al.* Abnormal conformation and impaired degradation of propylthiouracil-induced neutrophil extracellular traps: implications of disordered neutrophil extracellular traps in a rat model of myeloperoxidase antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis. Rheumatism.* 64(11), 3779–3787 (2012).
30. Trimarchi M, Miluzio A, Nicolai P *et al.* Massive apoptosis erodes nasal mucosa of cocaine abusers. *Am. J. Rhinol.* 20(2), 160–164 (2006)
31. Scheinberg MA, Bezerra JB, Almeida FA *et al.* Cutaneous necrotising vasculitisinduced by levamisole. *BMJ.* 1(6110), 408 (1978).
32. Tello N, Mateos-Parra JA, Díaz-Borjón A. Levamisole induced autoimmunity. *J. Arthritis.* 5(1), 187 (2016).
33. Khan TA, Cuchacovich R, Espinoza LR *et al.* Vasculopathy, hematological, and immune abnormalities associated with levamisole-contaminated cocaine use. *Semin. Arthritis. Rheum.* 41(3), 445–454 (2011).
34. de la Hera I, Sanz V, Cullen D *et al.* Necrosis of ears after use of cocaine probably adulterated with levamisole. *Dermatology.* 223(1), 25–28 (2011).
35. Schmidt KL, Mueller-Eckhardt C, Breithaupt H. HLA-B27, antinuclear antibodies and drug-induced agranulocytosis. *Klin. Wochenschr.* 56(23), 1189–1191 (1978).
36. Wiens MO, Son WK, Ross C *et al.* Cases: cocaine adulterant linked to neutropenia. *CMAJ.* 182(1), 57–59 (2010).
37. Czuchlewski DR, Brackney M, Ewers C *et al.* Clinicopathologic features of agranulocytosis in the setting of levamisole tainted cocaine. *Am. J. Clin. Pathol.* 133(3), 466 (2010).
38. Gómez-Puerta J. Antonio *et al.* Anti C1q antibodies. A promising biomarker for cocaine-levamisole induced vasculitis. *Reumatol. Clin.* 15(5), e66–e67 (2019).
39. Finkel JB, Marhefka GD. Rethin king cocaine-associated chest pain and acute coronary syndromes. *Mayo. Clin. Proc.* 86(12), 1198–**1**207 (2011).
40. Espinoza LR, Perez AR. Cocaine-induced vasculitis: clinical and immunological spectrum. *Curr. Rheumatol. Rep.* 14(6), 532–538 (2012).
41. Pearson T, Bremmer M, Cohen J *et al.* Vasculopathy related to cocaine adulterated with levamisole: A review of the literature - eScholarship. *Dermatol. Online. J.* 18(7), 1 (2012)
42. Patnaik S, Balderia P, Vanchhawng L *et al.* Is levamisole-induced vasculitis a relegated diagnostic possibility? A case report and review of literature. *Am. J. Case. Rep.* 16, 658–662 (2015).
43. Dezman Z, Rimi B, McClain J. Purpura and leukopenia in a cocaine user. *Clin. Toxicol (Phila).* 54(7), 601–602 (2016).
44. Larocque A, Hoffman RS. Levamisole in cocaine: unexpected news from an old acquaintance. *Clin. Toxicol (Phila).* 50(4), 231–241 (2012).
45. Gross RL, Brucker J, Bahce-Altuntas A *et al.* A novel cutaneous vasculitis syndrome induced by levamisole contaminated cocaine. *Clin. Rheumatol.* 30(10), 1385–1392 (2011).
46. Dy IA, Wiernik PH. Cocaine levamisole thrombotic vasculopathy. *Semin. Thromb. Hemost.* 38(8), 780–782 (2012)

47. Imbernón-Moya A, Chico R, Aguilar-Martínez A. Cutaneous mucosal manifestations associated with cocaine use. *Med. Clin (Barc).* 146(12), 544–549 (2016).

48. Trimarchi M. et al. Cocaine-Induced Midline Destructive Lesions Clinical, Radiographic, Histopathologic, and Serologic Features and their Differentiation from Wegener Granulomatosis. *Medicine.* 80(6), 391-404 (2001).

49. Carlson AQ, Tuot DS, Jen K *et al.* Pauci-immune glomerulonephritis in individuals with disease associated with levamisole-adulterated cocaine: a series of 4 cases. *Medicine.* 93(17), 290 (2014).

50. Bianco F. Iacovelli E, Tinelli E *et al.* Recurrent leukoencephalopathy in a cocaine abuser. *Neurotoxicology.* 32(4), 410–412 (2011).

51. Vosoughi R, Schmidt BJ. Multifocal leukoencephalopathy in cocaine users: A report of two cases and review of the literature. *BMC. Neurol.* 15, 208 (2015)

52. Ryan A, Molloy FM, Farrell MA *et al.* Fatal toxic leukoencephalopathy: clinical, radiological, and necropsy findings in two patients. *J. Neurol. Neurosurg. Psychiatry.* 76(7), 1014–1016 (2015).

53. Arora NP, Jain T, Bhanot R *et al.* Levamisole-induced leukocytoclastic vasculitis and neutropenia in a patientwith cocaine use: an extensive case with necrosis of skin, soft tissue, and cartilage. *Addict. Sci. Clin. Pract.* 7(1), 19 (2012).

54. Gulati S, Donato A. Lupus anticoagulant and ANCA associated thrombotic vasculopathy due to cocaine contaminated with levamisole: a case report and review of the literature. *J. Thromb. Thrombolysis.* 34(1), 7–10 (2012).

55. Peikert T et al. Functional Characterization of Antineutrophil Cytoplasmic Antibodies in Patients With Cocaine-Induced Midline Destructive Lesions. *Arthritis. Rheumatism.* 58(5), 1546–1551 (2008).

56. Ullrich K, Koval R, Koval E *et al.* Five consecutive cases of a cutaneous vasculopathy in users of levamisole adulterated cocaine. *J. Clin. Rheumatol.* 17(4), 193–196 (2011).

57. Arora NP. Cutaneous vasculopathy and neutropenia associated with levamisole-adulterated cocaine. *Am. J. Med. Sci.* 345(1), 45–51 (2013).

58. Metwally O, Hamidi M, Townsend L *et al.* The cocaine trail: levamisole-induced leukocytoclastic vasculitis in a cocaine user. *Subst. Abus.* 34(1), 75–77 (2013).

59. Colby TV, Tazelaar HD, Specks U et al. Nasal biopsy in Wegener's granulomatosis. *Hum. Pathol.* 22, 101-104 (1991).

60. Roberts JA, Chévez-Barrios P. Levamisole-induced vasculitis: a characteristic cutaneous vasculitis associated with extracellular alterated cocaine. *Arch. Pathol. Lab. Med.* 139(8), 1058–1061 (2015).