Clinical spectrum of small-vessel vasculitis related to cocaine consumption: data from an Italian cohort

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Cocaine, an illegal psychoactive tropane alkaloid, is often adulterated with levamisole, a veterinary anthelmintic: both substances are independently associated with the development of autoimmune phenomena. Ear-nose-throat (ENT) tract is commonly affected by lesions mimicking localised granulomatosis with polyangiitis (GPA), but symptoms and signs suggestive of systemic vasculitis have been reported too. Distinguishing these scenarios from an idiopathic form of ANCA-associated vasculitis (AAV) also represents a clinical challenge from an immune-serological perspective, as antineutrophil cytoplasmic antibodies (ANCA) are often detected. Herein we report the spectrum of clinical manifestations and histopathological features of 6 patients with history of cocaine consumption addressed to our Vasculitis Clinic (Table I).

Determining whether cocaine exposure induces AAV or whether patients develop unrelated idiopathic vasculitis is awkward. The pathogenetic mechanism involves vasoconstrictive effects of cocaine leading to compromised blood flow, immune activation triggering systemic inflammation, formation of immune complexes depositing on vessels, oxidative stress damaging endothelial cells, and direct injury caused by nasal inhalation, collectively promoting vascular inflammation and damage (1). Indeed, prolonged use causes marked inflammation with crusts and erosions of mucosal and cartilaginous structures (1). Subjects may develop septal and palatal perforation, a condition known as cocaine-induced midline destructive lesion (CIMDL), experienced by all our patients except one.

ENT region is the one typically affected and major organs are typically spared: none of our patients showed renal or pulmonary involvement, but suffered from skin lesions, dental apparatus and joint involvement.

The timeframe between last intake and clinical manifestations can vary widely, depending on dosage, frequency, individual sensitivity, and highlighting the question about whether cocaine could somehow sensitise our immune system to induce a vasculitis, maybe in response to an infectious or pharmacological trigger.

The prevalence of ANCA positivity in subjects who consume cocaine is high and might vary depending on levamisole concentration: autoimmunity workup usually shows a perinuclear (p-ANCA) staining pattern reactive against proteinase 3 (PR3) or atypical associated antigens, such as human neutrophil elastase (HNE), lactoferrin, and cathepsin G. The presence of anti-MPO together with anti-PR3 has been considered to be pathognomonic (2), as well as isolated high titres of MPO (3), although rarely found. Interestingly, in our cohort 3 patients (50%) had PR3 c-ANCA, an unusual finding if compared with literature data (4-6).

It is known that histopathological findings of inflamed nasal mucosa samples do not have any peculiar characteristics in these patients. On the other hand, just the evidence of necrosis, granulomatous inflammation and vasculitis can confirm the suspicion of GPA, but the presence of all these findings can be evidenced only in 15-25% of GPA patients with ETN involvement (7), thus the distinction between CIMDL and localised GPA remains challenging. All our patients underwent a bioptic procedure (5 nasal mucosa, 1 skin): granulomatous inflammation was not described in any specimen and evidence of vasculitis was certain only in two cases. Unspecific changes included: fibrinoid necrosis, eosinophilic/neutrophilic infiltrate, acanthosis. According to these findings, only one patient was eligible for ACR/EULAR 2022 criteria (8), whereas none fulfilled 1990 ACR/EULAR criteria (9).

Although complex, it is crucial to find the correct diagnosis to avoid ineffective immunosuppressive therapies in patients with a high infectious risk, in which cocaine cessation would be the only effective approach. Most patients can be effectively treated with high doses of corticosteroids, but this is not a sustainable long-term treatment option, and standard guidelines for AAV cannot be directly applicable to such patients. In conclusion, small-vessel vasculitis related to cocaine use should be suspected in case of ENT involvement, absence of multi-organ damage, negativity of inflammatory index, atypical ANCA positivity and lack of efficacy of traditional immunosuppressive drugs.

Table I. Demographic, clinical and serological data of patients.

Sex, age	Consumption*	Onset	Organ involvement	Symptoms duration before diagnosis (months)	Autoantibodies	Comorbidities	1990 / 2022 ACR/EULAR criteria	Previous therapies	Current therapies	Outcome
M, 53	Recent (within the last 3 months)	Skin ulcers	ENT, joints (arthritis), skin (ulcers)	> 48	Negative	None	No / No	BAR, CYC, ETN, LEF, MMF, MTX, RTX, PDN	MTX, PDN	Improvement
M, 53	Past (> 10 years)	Ear "fullness", nasal crusts	ENT	3	c-ANCA PR3	Obesity	No / Yes	AB, PDN	PDN, RTX	Improvement
F, 44	Past (> 10 years)	Nasal crusts, recurrent bacterial rhinitis	ENT, joints (arthralgias)	5	NE	Psoriasis	No / No	AB	None	Lost to FU
M, 46	Past (5 months)	Nasal crusts, epistaxis	ENT	5	c-ANCA PR3	Psoriasis, asthma	No / No	None	None	Lost to FU
M, 58	Present	Epistaxis	ENT (hearing loss), joints (arthralgias), skin (ulcers, gangrenous pyoderma), fever and malaise	3	p-ANCA then negative	AF/flutter, liver fibrosis, microcytic anaemia, OP, OSAS, skin and dental abscesses	No / No	MPDN, MTX, PDN, RTX	IVIG, PDN	Death
F, 36	Present	Dental abscesses and periodontitis, nasal crusts	ENT, dental apparatus	12	c-ANCA PR3	Asthma, cervical inflammatory myelitis	No / No	MPDN	Unknown	Lost to FU

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