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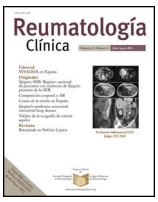

Letter to the Editor

Anti C1q antibodies. A promising biomarker for cocaine-levamisole induced vasculitis

Anticuerpos anti C1q. Un biomarcador prometedor para la vasculitis inducida por cocaína-levamisol

Dear Editor:

During the 1960s, Levamisole was used as an anthelmintic agent. It was subsequently found to have immunomodulatory effects and was used to treat several inflammatory disorders. During the last decade, attention has been focused on the use of levamisole as a cutting agent for cocaine and on several cases of severe agranulocytosis associated with cocaine use.[1]

Cocaine/levamisole-induced vasculitis – LIVEN – is a heterogeneous vasculopathy characterized by skin necrosis concentrated in acral areas [ears, cheeks, genitals and digital necrosis], retiform purpura, general symptoms and cytopenias.[2] Histopathological samples reveal pauci-inflammatory thrombotic diathesis accompanied with intravascular monocytes and evidence of complement activation.[3]

In 23 consecutive patients with systemic vasculitis from Hospital Universitario San Vicente Fundación, Medellín, Colombia, we analyzed the presence of Anti C1q antibodies, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, ($N=13$), polyarteritis nodosa ($N=4$), LIVEN ($N=4$) and Takayasu arteritis ($N=2$). Serum Anti-C1q were measured by ELISA techniques (QUANTA Lite, Inova, USA). This study was approved by the institutional review board at our institution.

From this small pilot study, we found that anti C1q antibodies were more prevalent in LIVEN patients in comparison with other vasculitis (75% vs. 5.3%, $p<0.001$). Mean anti C1q titers were significantly higher in patients with LIVEN than in other vasculitis (51.0 ± 25.3 vs. 10.4 ± 7.1 IU, $p=0.04$). Main clinical and serological characteristics including serum complement levels are summarized in Table 1.

It is well known that levamisole induces circulating autoantibodies. Patients commonly have high levels of perinuclear ANCA (p-ANCA) but not always against myeloperoxidase (MPO). p-ANCA titers are often directed against atypical p-ANCA-associated antigens within the neutrophil granules such as: human neutrophil elastase, lactoferrin, and cathepsin G.[4]

Recently, our group described a series of 11 patients with LIVEN.[5] ANCA (91%), lupus anticoagulant (73%), ANAS (45%), anti dsDNA (29%), anti Ro (29%) were most common autoantibodies.[5] Given the social difficulties for clinical follow-up in cocaine users, anti C1q antibodies are not measured yet in all patients with LIVEN attending our center.

Anti C1q antibodies have been described in many conditions including hypocomplementic urticarial vasculitis, systemic lupus erythematosus and membranoproliferative glomerulonephritis, among others. To our knowledge, this study is the first on anti C1q antibodies in patients suffering LIVEN.

C1q is a molecule important for the clearance of apoptotic cells. Apoptotic cells express autoantigens in their surface and may induce autoimmunity. Cocaine/levamisole generates repeated release of neutrophil antigens that might act as autoantigens and leads to decreasing tolerance. Neutrophils secrete complement proteins upon activation with PMA, fMLP and C5a. Neutrophil extracellular traps (NETs) have been implied as a potential source of autoantigens.[6] Leffler et al.[7] demonstrated that *in vitro* complement interaction with NETs and that C1q bound well and C3b deposited on NETs. The authors argue that decreased degradation of NETs led to deposition of complement and autoantibodies, recruitment of more complement, perpetuating the inflammatory cycle.

Finally, metabolic products of cocaine promote complement synthesis and lead to the deposition of C5b-9. LIVEN is proposed as a membrane attack complex (C5b-9) disease with enhanced apoptosis and prominent vascular expression of ICAM-1.[3]

Increasing reports signal that LIVEN is a contemporary public health problem. Recent reports from different authorities in the U.S. and the U.K. suggest that cocaine samples are contaminated

Table 1
Clinical and serological characteristics of LIVEN patients.

Case	Age/gender	Type of lesions	Autoantibodies	Serum complement[a]	Anti C1q antibodies	Treatment
1	17/male	Ear necrosis, retiform purpura on legs	Anti MPO	C3: Normal C4: Normal	Positive (20.3 IU)	PDN 30 mg/day
2	21/male	Rapidly progressive glomerulonephritis	Anti MPO, aCL IgG, aCL IgM, lupus anticoagulant	C3: Low C4: Low	Positive (116.4 IU)	PDN 60 mg/day Cyclo 1 g (pulses)
3	25/female	Ear necrosis, retiform purpura on legs	Anti MPO, aCL IgG	C3: Normal C4: Low	Positive (64.4 IU)	PDN 20 mg/day
4	36/male	Ear necrosis	ANAs, Anti dsDNA Anti MPO, Anti Ro	C3: Normal C4: Normal	Negative (3.1 IU)	MPDN 500 mg pulses plus PDN 40 m/day

Cyclo: cyclophosphamide, PDN: prednisolone, MPDN: methylprednisolone.

[a] Serum complement close to measurement of Anti-C1q antibodies.

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with levamisole in 50–80% of cases.[8] According to local authorities in Colombia, levamisole contaminates 40% of the market.[9] Indeed, preventing cocaine use is crucial for mitigating additional cases of LIVEN. Despite awareness of its toxicity by clinicians, identifying new biomarkers is necessary for practitioners that interface with these patients. Given our small sample size, further research is needed to confirm our findings that suggest anti C1q antibodies are useful markers in patients with LIVEN.

Conflict of interest

The authors declare no conflict of interest.

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