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Editorial

Vasculitides induced by cocaine and/or levamisole

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1. Introduction

Cocaine is the most widely used illicit stimulant in Europe. The number of individuals aged 15 to 34 years having used cocaine within the past year is estimated at 2.2 million, i.e., 1.9% of this age group [1]. The prevalence of cocaine use has increased steadily in Europe over the last three decades and is highest in Denmark, Spain, and the UK. Since 2010, however, cocaine use seems to have stabilized or declined.

The neuropsychiatric, infectious, and cardiovascular complications of cocaine use are well known. However, cocaine use has also been implicated in a variety of misleading presentations that simulate primary vasculitis, raising diagnostic challenges in two distinct situations, namely, cerebral vasculitis and ANCA-associated vasculitis (AAV). Fig. 1 illustrates a semantic analysis of abstracts retrieved from MEDLINE® by searching PubMed with the term "cocaine AND vasculitis". The results show that three different presentations can be distinguished.

Cerebral vasculitis is the first type of vasculitis for which a role for cocaine was suspected. Several cases of histologically documented cerebral vasculitis have been ascribed to cocaine [2]. The issue of cocaine-induced neurovascular lesions was probably obscured by the confusion between diffuse radiological cerebral vasculitis and true cerebral vasculitis, which cleared only when reversible cerebral vasoconstriction syndrome was described [3]. This situation will not be discussed here.

Diagnostic challenges occur due to the association between cocaine use and two distinct presentations of AAV. The first was identified in the 1990s and consists in upper respiratory tract lesions mimicking granulomatosis with polyangiitis (GPA), known as cocaine-induced midline destructive lesions (CIMDL) [4]. The second emerged abruptly in 2009–2010, when cases of skin necrosis and/or neutropenia with positive tests for ANCA were ascribed to the introduction on the North American market of cocaine cut with levamisole [5–7].

2. Cocaine-induced midline destructive lesions: GPA-like syndrome in cocaine users

2.1. Clinical presentation

This upper respiratory tract disorder affects regular cocaine users and is among the diagnoses considered in patient with destructive midfacial lesions, along with several infections (e.g., mycobacterial infections, syphilis, actinomycosis, leprosy, and mucormycosis), solid malignancies, nasal NK/T lymphoma, GPA, sarcoidosis, eosinophilic angiocentric fibrosis, and the very rare TAP deficiency syndrome.

Patients present with long-standing local and regional symptoms consisting of nasal obstruction, nosebleeds, and facial pain, without systemic manifestations [4]. The physical examination shows ulcerated, necrotic, and crusty lesions combined with destruction of the nasal septum and inferior turbinates. The sinuses are involved in 50% of cases. The lesions may extend centrifugally to the middle and superior turbinates, lateral walls of the nasal cavity, and hard and soft palates, which are very rarely involved in GPA (Fig. 2). Another difference with GPA is the absence of ear abnormalities and inflammatory orbital pseudotumor. However, infectious orbital cellulitis has been reported. The destructive bone lesions can extend to the base of the skull. By magnetic resonance imaging, involvement of the mucosa is combined with enlargement of the tonsils and, in some cases, collections of lymphatic fluid. Laboratory tests may show moderate inflammation.

Biopsies may demonstrate non-specific inflammatory and/or fibrotic lesions, leukocytoclastic and/or necrotizing vasculitis, and microabscesses. However, there are no granulomatous lesions, giant cells, or areas of deep necrosis [8].

2.2. CIMDL and ANCAs

ANCAs are highly prevalent: immunofluorescence testing is positive in 80% of patients with CIMDL, nearly always in a perinuclear pattern. Paradoxically, antibodies to myeloperoxidase (anti-MPO) are rare and anti-PR3 are found in nearly half the patients, in titers similar to those seen in true GPA. In 2004, Italian and American investigators reported that the ANCAs were chiefly directed to another serine protease, human neutrophil elastase (HNE) [9]. Anti-HNE were found in 70% to 85% of patients with CIMDL ($n = 25$), although sensitivity varied across assays from 54% to 67% (54–67%) and concordance was less than perfect. Anti-HNE had very high specificity, with positive results in only 1% of controls and no

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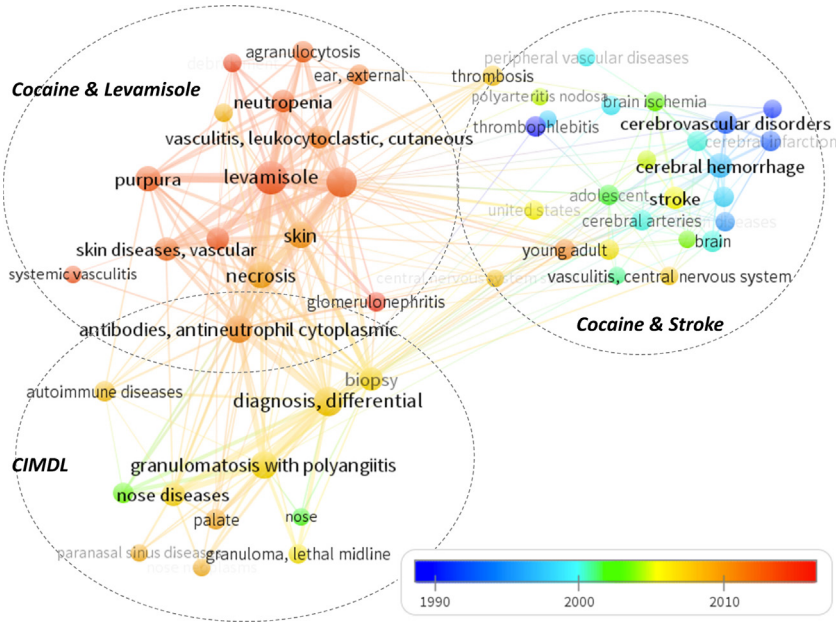

Fig. 1. Cocaine and vasculitis: bibliometric map. The semantics of the titles and abstracts retrieved from PubMed using the term "cocaine AND vasculitis" were analyzed using VOSviewer software [41]. Police size reflects the weight of the term. The distance between terms reflects the extent of co-location. The colored scale bar indicates the mean publication date or articles containing each term. CIMDL: cocaine-induced midline destructive lesions.

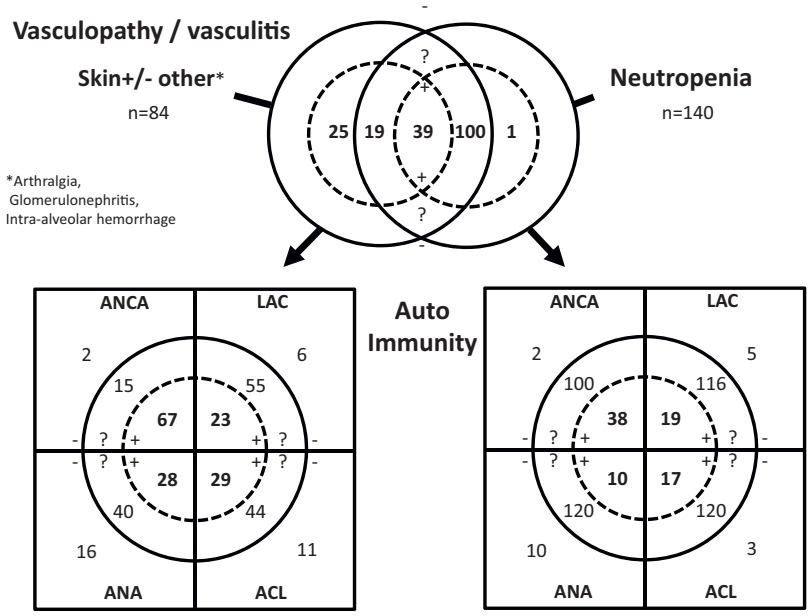

Fig. 2. Cocaine-induced midline destructive lesions. Computed tomography (A) and magnetic resonance imaging (B) showing destruction of the nasal septum, turbinates, and sinus walls. C. Progressive destruction of the palate over a 1-year period.

patients with GPA. Cross-inhibition tests established that the dual reactivity to PR3 and HNE was not related to cross reactivity.

2.3. Pathogenesis

CIMDL is rare, suggesting a role for patient-related factors other than the cocaine use profile. The initial local insult probably originates in local irritation of the mucosa by the cocaine crystals, combined with ischemic necrosis and bacterial superinfection. In addition, caspase 3 and 9 expression indicating apoptosis has been found within CIMDL lesions but not GPA lesions, nasal polyposis specimens, or biopsies from healthy controls. In vitro, cocaine exhibited a dose-dependent and time-dependent pro-apoptotic effect on HaCat cells derived from keratinocytes [8]. Whether the anti-PR3 or anti-HNE ANCAs contribute to perpetuate the lesions is unclear. HNE is a serine protease with documented deleterious effects in many inflammatory respiratory tract diseases such as asthma, chronic obstructive lung disease, and cystic fibrosis. These effects are ascribable to a pro-inflammatory influence combined with an ability to degrade the extracellular matrix. In patients

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