Cocaine induced midline destructive lesions*

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Summary

Purpose: Review of the literature concerning cocaine induced midline destructive lesions (CIMDL).

Methods: We reviewed the English literature regarding CIMDL involving the nose and its surrounding structures. The review is based on a search of the US National Library of Medicine (PubMed) online database from January 1st, 1982 to March 31st, 2013.

Results: CIMDL is a pathology that mimics systemic diseases with positive anti-neutrophil cytoplasmic antibodies (ANCA). The prevalence of CIMDL is considered to be about 4.8% among cocaine users. Clinical manifestations include hyposmia, facial pain, crusting, ulcers, nasal septal perforation, palatal perforation, sinus wall destruction, orbital erosion and damage of the anterior skull base. The presence of ANCA directed against human neutrophil elastase (HNE) is the most distinguishing feature of CIMDL. Toxicological tests, indirect immunofluorescence microscopy, antigen specific solid assay testing, histopathological analysis, apoptosis assay and MRI imaging concur in the clinical identification of CIMDL. The pathogenesis of CIMDL is poorly understood and implicates inflammatory, infective, proapoptotic and autoimmune mechanisms.

Conclusion: CIMDL must be readily recognized by clinicians to provide appropriate treatment. Immunosuppressive therapy has no role in the treatment of CIMDL. Only abstinence can interrupt the progression of the disease.

Key words: cocaine, nose, lethal midline granuloma, nasal septal perforation, palate

Introduction

The association of cocaine with rhinological practice dates back to the 19th century, when the uniquely combined anaesthetic and vasoconstrictive properties of cocaine were discovered [(1)]. Along with the practical advantages of intranasal medical use of cocaine came the drawbacks of intranasal cocaine use, namely systemic side effects and addiction [(2)]. Nowadays, cocaine is one of the most trafficked illicit drugs in the world [(3)]. The majority of European cocaine consumers (65%) report intranasal inhalation ("snorting" or "sniffing") of cocaine crystals as the main route of administration [(4)]. The nose, as a consequence, is often routinely exposed to the detrimental effects of cocaine and adverse effects on the nasal tract are frequent [(5)].

Cocaine induced midline destructive lesions

Cocaine induced midline destructive lesion (CIMDL) is a pathology that mimics systemic diseases with positive anti-neutrophil cytoplasmic antibodies (ANCA), radiographical abnormalities of mid-facial structures and evident histopathological alterations [(6)]. Prevalence of CIMDL is unknown but data from the United States Department of Health and Human Services indicate that the prevalence of nasal isolated septal perforation, the most common clinical presentation of CIMDL among habitual cocaine abusers [(7)], is about 4.8% [(8)].

We reviewed the English literature regarding CIMDL involving the nose and its surrounding structures. The review is based on

a search of the US National Library of Medicine (PubMed) online database from January 1st, 1982 to March 31st, 2013. The search was based on the following keywords: "cocaine nose", "cocaine sinus", "cocaine palate", "cocaine orbit", "cocaine nasolacrimal", "cocaine eye", "cocaine lesion" and "cocaine review". The number of papers documenting cases of CIMDL and the number of affected patients described are reported in Table 1. For each publication we analyzed clinical, histopathological, serological and radiological findings, therapies and outcomes. We then summarized the information in a Table, which is available as a supplementary Table online (http://www.rhinologyjournal.com).

Clinical presentation

Individuals affected by CIMDL usually present non-specific signs and symptoms that are shared with other systemic diseases such as infections, neoplasms and autoimmune or granulomatous diseases [6]. Fever, malaise weight loss, arthralgia or myalgias are usually absent in CIMDL patients, indicating non-systemic disease [9]. The main complaints are usually chronic nasal obstruction, hyposmia, epistaxis and severe facial pain [6,7]. Common findings include nasal septal perforation, diffuse necrotizing ulcerative lesions, and crusting (Figure 1b) [7,10-68]. Complete or near total loss of the nasal septum (Figures 1b, 2c, 2d, 3b and 3d) was described in 23 cases [7,13,15,17,20-23,25,28-31,34,37,39,41,45,47,48,64,66,67] and 13 of these patients also presented nasal deformity (Figure 2a), saddle nose or loss of nasal projection [7,13,15,17,28,30,39,41,47,48,58,63,67].

External cutaneous ulcers of the nose and surrounding areas are also described and involve the subnasal sulcus and philtrum (Figure 4a) [20,32,39,41,49], the nostril tip and the nasal soft triangle [59]. External facial or nasal erosion has been observed in the columellar area (Figure 4b and 5a) [39,41,67,69] and in the area of the upper lip, premaxillary soft tissues and alar nasal cartilage (Figure 3a) [41]. Other described features are upper lip swelling and phymatoid enlargement of the nose [62] and crack-cocaine associated acute necrosis of the nose and upper lip, with necrotizing infection of the subcutaneous soft tissue of the cheeks, forehead and temporal region [70].

Centrifugal internal extension of the lesions and erosion of middle and superior turbinates occur in more severe cases [7], and are often reported [7,15,16,21,23,25,29,31,32,34,41,45,63]. Further expansion of CIMDL can involve the lateral wall [23,29,34,41,45,57,61,64,66,71,72,73] or the floor of the nasal cavity causing hard and soft palate perforations (Figure 1a, 1b, 3b and 3c), documented in 35 reports, that can give rise to dysphagia, rhinolalia and oro-nasal reflux [7,14,15,21,25,26,28-30,33,36-39,40,41,45,47,48,51-53,55,60,63,68,69,74,75,76-82]. Symptoms also include lack of sensitivity sensation, anosmia, pain in the nasal passages, headache and halitosis [74]. The majority of palatal perforations are located in the hard palate or combine hard and soft palate involvement, while soft palate presentations account for 5.5% of cases [74].

Table 1. Midline lesions in cocaine abusers 1982-2013.

Midline lesions in cocaine abusers 1982-2013	
Number of reports	75
Number of patients	164
ANCA§ test	24
ANCA pattern evaluation*	21
ANCA antigen specificity**	5
Medical therapy	22
Surgical reconstruction	23
Prosthetic management	12
Biopsy/Histopathology	36

§ Anti-neutrophil cytoplasmic antibodies.

* Number of papers reporting ANCA pattern evaluation with indirect immunofluorescence.

** Number of papers reporting ANCA antigen specificity evaluation with antigen specific solid assay testing.

Pharyngeal wall ulceration has also been reported in three cases [14,25,75]. These findings offer an important clue for the diagnosis of CIMDL, since this syndrome reaches an extent of local destruction that is unlikely in other systemic diseases [6,7].

A case series by Alexandrakis et al. [31]) reported seven cases of nasolacrimal duct obstruction (NLDO) associated with intranasal cocaine abuse. Three of the patients also presented destruction of the orbital bony walls and secondary orbital cellulitis [31]. Expansion of CIMDL to the walls and contents of the orbit was reported in another eight cases [23,31,41,44,61,72,73,83]. Damage ranged from dehiscence of the lamina papyracea [23] or of the orbital floor [72] with no visual symptoms to more severe ocular conditions, such as chronic orbital inflammation, double vision, reduced visual acuity, ocular motility impairment, pseudotumor and optic neuropathy [9,44,61,73]. Severe centrifugal expansion of CIMDL eroded the anterior skull base in three cases [41,60,64] causing encephalocele. In one case, a less severe lesion opened a small fistula in the skull base, causing acute diffuse pneumocephalus [66]. Clinical manifestations included altered mental status, severe headache, anxiety, confusion, cerebritis and meningitis [7,41,60,64,66]. In another case the erosive process reached the sphenoid bone posteriorly and damaged the pituitary gland, causing panhypopituitarism [57].

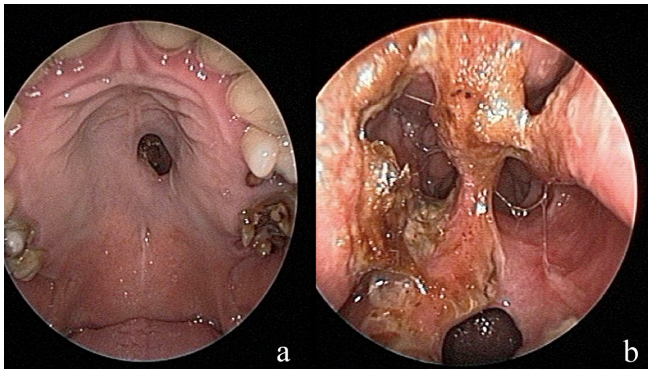

Figure 1. The picture shows a hard palate perforation (a) and extensive necrosis and crusting in an oro-nasal cavity where much of the hard palate and of the nasal septum are missing.

Imaging

Radiographical evaluation of patients with CIMDL does not provide conclusive evidence for diagnosis of CIMDL. A CT scan in severe cases can show a centrifugal progression of the destruction, along with bone and cartilage damage extension. Magnetic resonance imaging (MRI) with contrast medium provides more information in CIMDL [7,84]. Affected portions of nasal and paranasal mucosa are visible on MRI as hypointense areas on T2, and show reduced or non-uniform enhancement [41]. MRI is also useful to map the areas of soft tissue erosion. In particular, both CT and MRI examinations of hard palate perforations were correlated with the destruction of bilateral inferior or bilateral middle turbinates in a series of 18 CIMDL patients [7]. These observations led to the definition of a centrifugal pattern of erosion in CIMDL that was corroborated by clinical findings [7,52].
Another described MRI finding is diffuse swelling of palatine and pharyngeal tonsils characterized by small fluid collections embedded in lymphatic tissue [7]. Radiological signs of otitis media were identified as well [41]. All the described radiological findings are not disease-specific, but provide ancillary information that helps to better define local extension of CIMDL and possible treatment strategies [6,41].

Laboratory testing

Patients with suspected CIMDL are generally not keen to admit or discuss cocaine consumption and, even when they admit cocaine use, they tend to minimize or even deny their addiction [85]. Positive testing of urine, blood or hair samples for cocaine metabolites can be a useful clue, and it can raise the suspicion of CIMDL in a patient presenting with non-specific signs and symptoms that resemble other systemic diseases [6].
Indirect immunofluorescence microscopy (IIF) and antigen specific solid assay testing have been used since the beginning of 2004 as a tool for differential diagnosis between CIMDL and

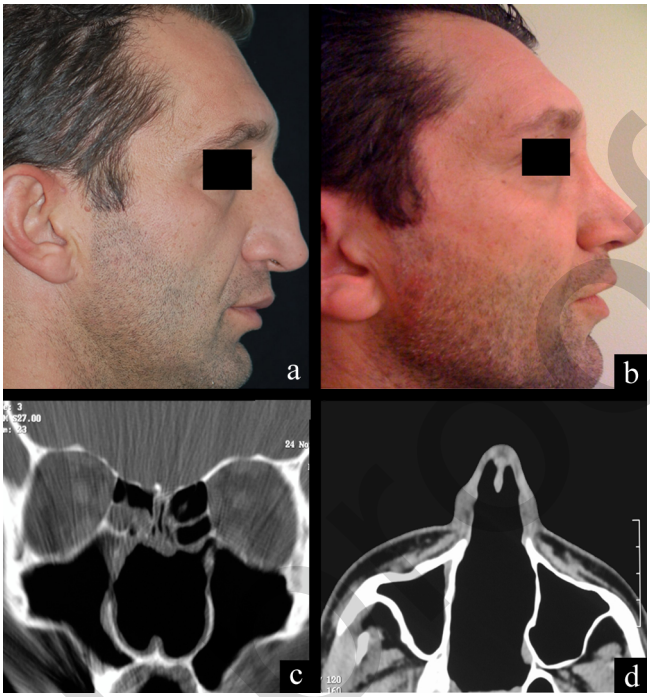

Figure 2. The picture shows an example of cocaine related nasal deformity (a), its surgical correction outcome (b) and coronal (c) and axial (d) Computed Tomography (CT) findings from the same patient, showing loss of the nasal septum and of the turbinates.

various forms of vasculitis, most prominently granulomatosis with polyangiitis (Wegener's, GPA) [86]. However, evaluation of ANCA with IIF was described only in 21 of 75 publications, and ANCA specificity assays were performed only in 5 cases, as summarized in Table 1.
Positive anti-neutrophil cytoplasmic antibodies in indirect immunofluorescence microscopy are frequent in CIMDL [86]. These antibodies, when tested with antigen specific solid assays, specifically and primarily react with human neutrophil elastase (HNE), also known as human leukocyte elastase (HLE), and display a perinuclear staining pattern (p-ANCA) [87]. Furthermore p-ANCA in CIMDL does not react with myeloperoxidase (MPO) like p-ANCA in a minority of GPA [6]. However, proteinase 3 (PR3) specific ANCA with cytoplasmic staining pattern (c-ANCA), which is typical of GPA, can be found in about 50% of ANCA positive CIMDL patients [86,87]. Undoubtedly, PR3-cANCA positivity in the absence of other clinical and diagnostic signs poses a genuine differential diagnostic challenge that can, however, be overcome through HNE-specific solid assay testing [6], as discussed in the differential diagnosis section of this review.

Apoptosis assay

The apoptotic effect of cocaine has been observed in several in vitro and animal studies, while only one study has demonstrated increased apoptosis in tissue samples from CIMDL patients [88]

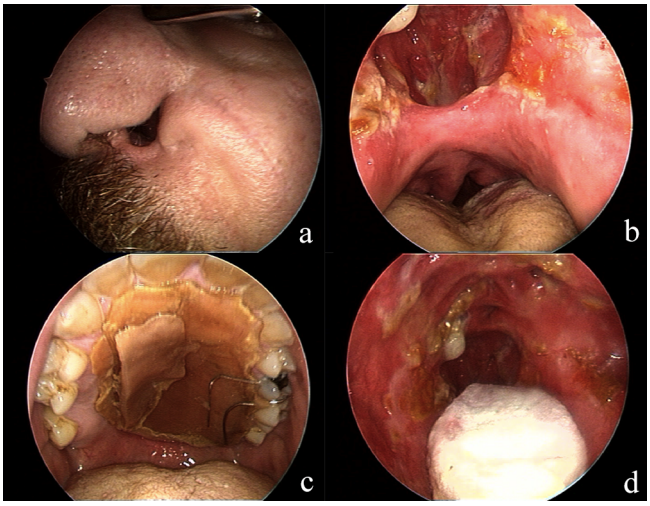

Figure 3. The picture shows cocaine induced damage to the ala nasi (a), a wide palatal perforation (b) and its prosthetic obturation seen from the oral cavity below (c) and from the nasal cavity above (d), where the nasal septum is missing.

compared to healthy and GPA controls. Unfortunately, tissue samples from chronic cocaine abusers not affected by CIMDL who represent the ideal control population to determine the specificity of an apoptosis assay were not available [88].
Identification of apoptotic cells in nasal mucosa samples using a commercially available in situ terminal deoxynucleotidyl transferase-mediated dUTP-digoxygenin nick end labelling (TUNEL) cell death detection kit, reveals a substantially higher number of apoptotic cells in CIMDL compared to GPA, nasal polyposis and healthy controls [6].

Histopathology

Histopathological analysis should be performed on multiple biopsy specimens taken from the margins of the lesion, which are more likely to contain diagnostic tissue, rather than from the necrotic centre of the lesion [6]. Biopsies and histopathological studies in CIMDL were performed by 36 authors (48%) of the reports analyzed in this review.
CIMDL does not have disease-specific histopathological features, as many are also common to GPA, which constitutes CIMDL's primary histopathological differential diagnosis. CIMDL and GPA share the following histological manifestations: mixed inflammatory infiltrates, microabscesses in vascular walls, perivenulitis, vascular microthrombotic changes, leukocytoclastic vasculitis and fibrinoid necrosis [7]. Nonetheless, histopathological examination can identify lesions that are typical of GPA, thus excluding the presence of CIMDL. Pathognomonic lesions for GPA are stromal granulomas with giant cells, microabscesses and deeply located necrosis [6,7]. These three features, when found in the biopsy specimen, make histopathological differentiation between GPA and CIMDL possible, while in their absence

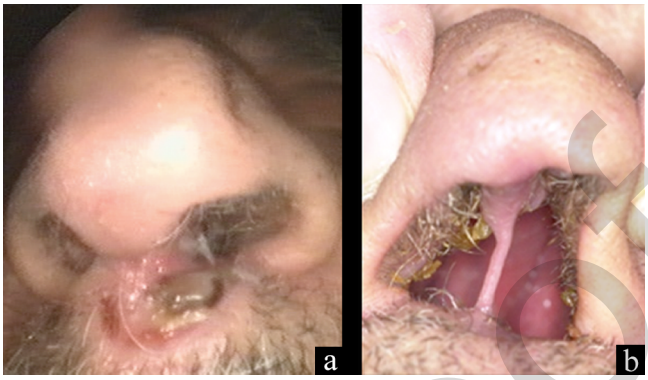

Figure 4. The picture shows cocaine related damage to the subnasal sulcus and philtrum (a) and destruction of the columella (b).

histopathological differentiation is impossible [6]. Finally, it should be noted that only 50% of GPA patients with nasal involvement show the typical histopathological diagnostic features of GPA on nasal biopsy specimens [6].

Differential diagnosis

Many different conditions other than cocaine abuse can cause midline destructive lesions, such as infections, neoplasms, systemic diseases and exposure to chemicals [6,7,89-91].
The patient's history should be carefully analyzed to rule out traumatic causes such as surgery, accidental traumas or self-inflicted lesions (nose picking) [42,86]. Infections such as tuberculosis, tertiary syphilis [76], mucormycosis in immunocompromised patients [92] and septal abscesses should be considered when approaching midline destructive lesions [6]. Other rare infective causes of midline destructive lesions are leishmaniasis [93], typhoid, diphtheria and leprosy [15]. Identification of bacterial or fungal nasal perforations is usually straightforward and based on examination and laboratory tests. Both solid and haematological tumours, such as NK/T cell, peripheral T cell and diffuse large B cell lymphoma, can cause midline destructive lesions and can be identified through laboratory tests and histopathological analysis [94].

Many immune system disorders can give rise to midline destructive lesions, including systemic lupus erythematosus (SLE) [89], sarcoidosis, rheumatoid arthritis, polyarteritis nodosa, mid-facial granuloma syndrome and GPA [6]. Among these conditions, the differentiation of CIMDL from GPA with limited nasal or sinus involvement is challenging, especially in patients who deny their cocaine addiction. Upon examination, patients with CIMDL usually present a higher degree of local destruction compared to nasal limited GPA [7]. In addition, centrifugal expansion of the lesion from the nasal septum to the nasal walls is a frequent finding in CIMDL patients [7]. In contrast, GPA tends to present with other disease markers and isolated nasal GPA is uncommon [6]. In such cases, histopathological analysis can show, in about 50% of

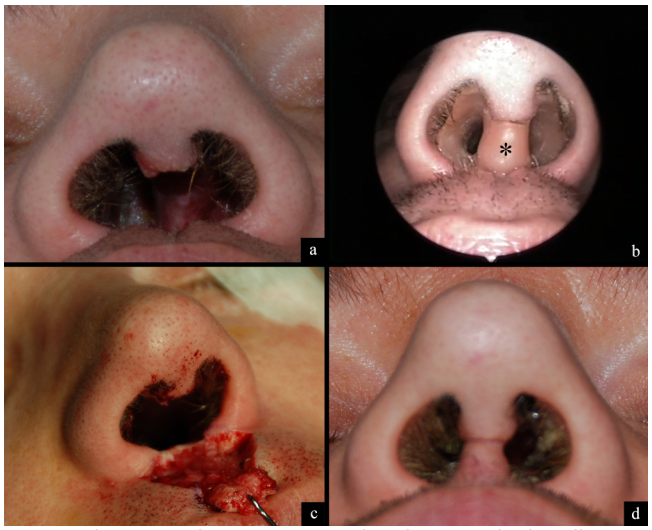

Figure 5. The picture shows a cocaine induced near-total columellar erosion associated with an anterior perforation of the nasal septum (a) that underwent prosthetic management (b) with a plastic columella (*) and later was treated surgically (c) with a local labial advancement flap with satisfactory outcomes (d).

patients [95], the typical diagnostic features of GPA that we have already described.
However, CIMDL and GPA can be more easily distinguished through IIF and antigen specific solid assay testing. Presence of p-ANCA reacting with HNE and not with MPO identifies CIMDL, regardless of the presence of c-ANCA directed against PR3 [6].
On the other hand, the mere presence of c-ANCA that reacts with PR3 is characteristic of GPA [96], while HNE-p-ANCA is usually not found in GPA [87]. A small proportion of GPA patients test positive for MPO-p-ANCA or test negative for ANCA altogether; these two latter possibilities always need to be considered when testing for GPA [6].

An investigation of the use of MRI in differential diagnosis of CIMDL compared findings between a group of 18 CIMDL and 21 GPA patients [7]. Although signal alterations on T2 were not specific for CIMDL, as already mentioned, it was noted that overall severity of tissue destruction was greater in CIMDL, in accordance with clinical observations. Moreover, when only the mucosa of the nasal septum and turbinates was considered, reduced or non-uniform enhancement was significantly more frequent in CIMDL patients than in GPA [7].

Pathogenesis

The pathogenesis of CIMDL is poorly understood and implicates inflammatory, infective, proapoptotic and autoimmune mechanisms [88]. The low incidence of nasal septal perforation, the most common form of CIMDL among cocaine abusers, demonstrates the relative rarity of CIMDL among cocaine users. Thus, individual predisposing factors must be implicated in the multifaceted pathogenesis of CIMDL.
All chronic cocaine users seem to be similarly subject to the local ischaemic and irritating effects of cocaine crystals [88]. The consequent diffuse crusting and resultant traumatic removal of tightly adhering scabs, often performed with foreign bodies such as pens or pencils or even the articulating arm of an umbrella [42,74], should affect all cocaine users similarly. Likewise, bacterial superinfections of damaged nasal mucosa should differently affect cocaine users based on their individual level of local mucosal damage [6]. Individual hygienic and antibiotic treatment habits should also be taken into account. Considering the extent of midline erosion in CIMDL, it is not surprising that bacterial superinfections have been demonstrated in almost all patients with CIMDL [7].
One possible explanation of the destructive effects of cocaine may be the time and dose dependent apoptotic effect of cocaine on nasal mucosa [88]. While an increased cellular apoptotic rate could represent a convincing cause of CIMDL, there is little evidence to implicate a role for apoptosis in the nasal mucosa of cocaine abusers who do not present CIMDL.

The presence of ANCA is the only clear distinguishing feature between patients with CIMDL and cocaine abusers with similar use patterns but without CIMDL [86]. The presence of ANCA characterizes the phenotype of CIMDL [6], but the role of ANCA in the onset and progression of CIMDL is not clear. Functional characterization of the interaction of HNE-ANCA with the proteolytic activity of HNE and with HNE natural inhibitors did not demonstrate any relevant correlations [87].

Therapy

Treatment of CIMDL is a difficult task, made even more problematic by the widely acknowledged poor compliance of cocaine abusers [41]. After the diagnosis is communicated to the patient, it is important to clarify the nature and the evolution of CIMDL before discussing potential treatment options. Immunosuppressive therapies do not have a role in the treatment of CIMDL [6,7], and the complex pathogenetic mechanisms causing CIMDL can only be interrupted by discontinuing cocaine abuse. Continued abstinence, in fact, is an absolute requirement that patients must fulfil to consider surgical reconstruction [6]. If the patient reliably quits sniffing, medical therapy, reconstructive surgery (Figure 2b, 5c and 5d) and prosthetics (Figure 3c, 3d and 5b) can achieve satisfactory results [31,35,41,46,58,63,66,67,76,78,81]; otherwise, surgical intervention is destined to failure [23,29,52,75,97].
Conservative treatment is based on regular saline douches, careful debridement of necrotic tissues and crusts and administration of systemic or topic antibiotic therapy [41].
Prosthetic closure of oro-nasal fistulae (Figure 3c and 3d) reduces the burdensome effects of oro-nasal reflux [75,76]. Palatal obturator prosthesis can be a non-invasive, early treatment choice for

patients who are beginning their abstinence period [39]. After an adequate abstinence period, surgical correction of mucosal or cutaneous defects is possible.

Among CIMDL patients, the most frequently required surgical procedures include closure of septal or palatal perforations or skull base defects [29,35,41,45,46,52,58,60,67,77,98]. Patients with a heavier disease burden can ask for rhinoplasty (Figure 2a and 1b) or closure of naso-cutaneous fistulae [58,67,99]. Both local and revascularized free flaps are used in CIMDL reconstructive surgery, depending on the size of the lesions [29,35,41,45,46,52,58,60,66,67].

Medical therapy, surgical reconstruction and prosthetic management are therefore the main treatment options; Table 1 shows the number of studies describing their application in CIMDL.
The adequate length of the abstinence period needed to perform surgery safely and effectively is still debated. Some authors require at least 6 months of negative toxicological tests negativity [39,52,65,76]; others prefer to perform surgery after a 12 months period of demonstrated abstinence [15,33,41].

Conclusion

CIMDL is a complex syndrome that occurs in a small proportion of cocaine abusers. Nonetheless, CIMDL must be readily recognized by clinicians to provide appropriate treatment. Signs and symptoms are non-specific and common to many systemic diseases. In a wide spectrum of differential diagnosis, GPA is the disease that is most difficult to differentiate from CIMDL. Toxicological tests, IIF microscopy, antigen specific solid assay testing, histopathological analysis, TUNEL assay and MRI imaging concur in the clinical identification of CIMDL.
The presence of HNE-ANCA is the most distinguishing feature of CIMDL. HNE-ANCA is important in the definition of CIMDL pathogenesis, but also represents an important diagnostic tool. However, as shown in Table 1, indirect immunofluorescence microscopy, antigen specific solid assay testing and histopathological analysis are not consistently performed, but correct diagnosis was achieved in all the cases of CIMDL included in our review and no cases of mismanagement were reported.
Immunosuppressive therapy has no role in the treatment of CIMDL. Only abstinence can interrupt the progression of the disease and, when sufficiently prolonged, represents a necessary condition for successful surgical reconstruction.

Authorship contribution

MT wrote, supervised and revised the work and guided the bibliographic research, GB wrote the article and contributed to the bibliographic research, MB supervised the work and provided some of the pictures.

Conflict of interest

The authors declare no conflict of interest.

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