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Maxillofacial surgery

Palate perforation differentiates cocaine-induced midline destructive lesions from granulomatosis with polyangiitis

La perforazione del palato differenzia le lesioni destruenti della linea mediana indotte da cocaina dalla granulomatosi con poliangioite

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SUMMARY

Cocaine abuse occasionally causes extensive destruction of the osteocartilaginous structures of the nose, sinuses and palate, which mimics the clinical picture of other diseases associated with necrotising midfacial lesions. The differentiation of cocaine-induced midline destructive lesions (CIMDL) and limited granulomatosis with polyangiitis (GPA) may be difficult, particularly if patients do not readily admit substance abuse. We studied 10 patients with CIMDL and palate perforation referred to our Unit between 2002 and 2015. All cases underwent nasal endoscopy, sinus CT or MRI and ANCA test. In 8 patients, a nasal biopsy was performed. The PubMed database was searched to review all cases of palate perforation described in patients affected by CIMDL or GPA. All 10 cases presented with septal perforation and inferior turbinate destruction. We found hard palate perforation in 7 patients, soft palate perforation in 2 patients, and perforation of both in one patient. ANCA testing was negative in 8 patients and positive in 2, with C-ANCA and P-ANCA specificity, respectively. A review of the English literature identified palate perforation in 5 patients with GPA and in 73 patients with CIMDL. The presence of palate perforation in patients with MDL may represent a clinical marker that strongly favors CIMDL over GPA.

KEY WORDS: Palatal perforation • Cocaine • Granulomatosis with polyangiitis (GPA)

RIASSUNTO

L' abuso di cocaina può talvolta causare lesioni destruenti della struttura osteocartilaginea del naso, dei seni paranasali, del palato, con caratteristiche cliniche che ricordano altre patologie sistemiche associate a lesioni necrotizzanti centrofacciali. La diagnosi differenziale tra lesioni destruenti della linea mediana indotte da cocaina (CIMDL) e granulomatosi associata a poliangioite (GPA) può essere complessa, in particolare se il paziente non ammette l'abuso di sostanze. 10 pazienti con CIMDL e perforazione palatale sono stati trattati presso la nostra Unità Operativa tra il 2002 ed il 2015. Tutti i casi sono stati sottoposti ad endoscopia nasale, TC o RMN del massiccio facciale ed Anca test. In 8 casi è stata effettuata anche la biopsia nasale. Contestualmente è stata eseguita una revisione della letteratura presente su PubMed riguardante i casi di perforazione palatale in pazienti affetti da CIMDL e GPA. Tutti i 10 pazienti oggetto dello studio presentavano perforazione palatale e distruzione dei turbinati inferiori; inoltre 7 pazienti presentavano perforazione del palato duro , 2 pazienti perforazione del palato molle ed 1 paziente perforazione di entrambi. Gli Anca test erano negativi in 8 pazienti e positivi in 2, sia per C-Anca sia per P-Anca. La revisione della letteratura edita in lingua inglese ha evidenziato perforazioni palatali in 5 pazienti affetti da GPA e in 73 pazienti affetti da CIMDL. La presenza di perforazione palatale in pazienti con lesioni destruenti della linea mediana può rappresentare un nuovo marker clinico a favore delle CIMDL nella diagnosi differenziale con GPA.

PAROLE CHIAVE: *Perforazione del palato • Cocaina • Granulomatosi con poliangioite (GPA)*

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Introduction

The United Nations Office on Drugs and Crime reports that cocaine use has remained stable during the last three years, with 14 to 21 million estimated users per year worldwide. In particular, cocaine use has remained high in North America (5 million), South America (4.5 million), Africa (2.8 million), and Western and Central Europe (4 million) [1]. In the last 2016 European Drug Report, it was estimated that around 17 million adults (15-64 years) have used cocaine at least once in their lifetime with some countries (such as Spain and UK) showing a prevalence of use among young adults (15-34 years) that matches or even exceeds rates in the USA [2].

The most frequently used route of cocaine administration

is intranasal inhalation, or "snorting", and thus adverse effects on the nasal tract are very common [3]. Habitual nasal insufflations of cocaine may cause mucosal lesions, and if cocaine use becomes chronic and compulsive, progressive damage of the mucosa and perichondrium leads to ischaemic necrosis of septal cartilage and perforation of the nasal septum [4]. Occasionally, cocaine-induced lesions cause extensive destruction of the osseocartilaginous structures of nose, sinuses and palate that can mimic other diseases such as tumours, infections and immunological disorders. Several problems have been reported in differentiating cocaine-induced midline destructive lesion (CIMDL) from granulomatosis with polyangiitis (GPA) with limited ear-nose-throat involvement (ENT) [5]. An essential element for achieving correct diagnosis is clinical history, although cocaine abusers rarely admit drug dependency. The presence of a positive ANCA test with either proteinase 3 (PR3) or myeloperoxidase (MPO) specificity facilitates differential diagnosis of GPA from CIMDL, although not in all cases.

In the present study, we focus on patients with CIMDL and palatal perforation and review the available literature to discuss the utility of this type of midface destructive lesion as a possible clinical marker that might orient differential diagnosis.

Materials and methods

A series of 10 patients with CIMDL and palate perforation evaluated at the Department of Otorhinolaryngology of San Raffaele Hospital between February 2002 and October 2015 was retrospectively reviewed. This retrospective study adhered to ethical standards according to the Declaration of Helsinki. The patients ranged in age from 28 to 60 years; there were 8 males and 2 females. Follow-up lasted from 8 to 86 months. The duration of cocaine abuse was available in 7 patients, ranging from 2 to 30 years, at doses varying from 1 to 10 g/week. Demographics and past medical history were collected at the initial visit. It is important to underline that data concerning duration and daily dose of cocaine abuse are difficult to estimate because of poor collaboration between cocaine abusers and physicians. All patients underwent physical examination at the outpatient clinic of our Institute that included inspection of the face, oral cavity and oropharynx, as well as inspection of the nasal cavities and nasopharynx using 30° rigid telescopes (4 mm in diameter). During endoscopy, biopsies and samples for bacterial and fungal cultures were taken. A total of 8 mucosal biopsy specimens were evaluated. Sections were stained with haematoxylin-eosin. Orcein staining was used to evaluate elastic fibres, and periodic-acid Schiff and Ziehl-Nielsen stains were used to identify fungi and mycobacteria, respectively. Ten patients underwent imaging studies; in particular, 7 patients were evaluated using computed tomography (CT) scan, and 3 patients with magnetic resonance imaging (MRI). Sera from 10 patients were tested for ANCA in the laboratory at our Institute. We used indirect immunofluorescence (IIF) microscopy on ethanol-fixed blood donor neutrophils following the standard procedure outlined at the first ANCA workshop [6]. The PubMed database was searched for the available English literature (original papers, case series, and single reports) describing palate perforation in cocaine abusers and in patients suffering from GPA (available at: http://www.actaitalica.it/issues/2017/4-2017/06_TRIMARCHI).

Results

The 10 patients in our study cohort presented with a variable combination of common symptoms, such as epistaxis, oro-nasal regurgitation of solids and liquids, dysphagia, oropharyngeal pain, nasal speech and halitosis. At rhinoscopy, all patients showed necrotising ulcerative lesions, extensive crusting, intranasal destruction of the vomer and perforation of the nasal septum cartilage as well as of the hard and/or soft palate. Eight patients presented destruction of inferior turbinates, 7 of middle turbinates, and one of the right superior turbinate. The medial wall of maxillary sinus was completely reabsorbed in one patient. Oro-nasal communication affected the hard palate in 7 cases, the soft palate in 2 cases, and both the soft and hard palate in one patient. The diameter of the oro-nasal fistula ranged from 1 to 4 cm (Figs. 1, 2).

All patients had positive nasal cultures for *Staphylococcus aureus*. No positive fungal cultures were observed. Eight biopsies were negative for inflammatory, oncological and immunological diseases (2 patients admitted cocaine use, but did not consent to biopsy). One patient showed strong P-ANCA positivity on immunofluorescence with negative ELISA for both anti-PR3 and anti-MPO antibodies. One patient showed C-ANCA positivity on immunofluorescence with positive ELISA for anti-MPO antibodies.

CT scan confirmed the endoscopic features, showing perforation of nasal septum and palate, and destruction of the inferior middle and superior turbinate, whereas MRI revealed areas of abnormal signal in the septal and palate perforation, such as hypointensity of mucosal and submucosal tissue and nonhomogeneous enhancement.

Discussion

CIMDL represents an uncommon complication of habitual intranasal cocaine insufflations [7]. Patients with CIMDL develop extensive destruction of midfacial osseocartilaginous structures, which can resemble different pathological conditions such as oncologic, infectious and immunological diseases [5]. If differential diagnosis between oncologic or infectious disorders and CIMDL is facilitated by histopathological features and microbiological

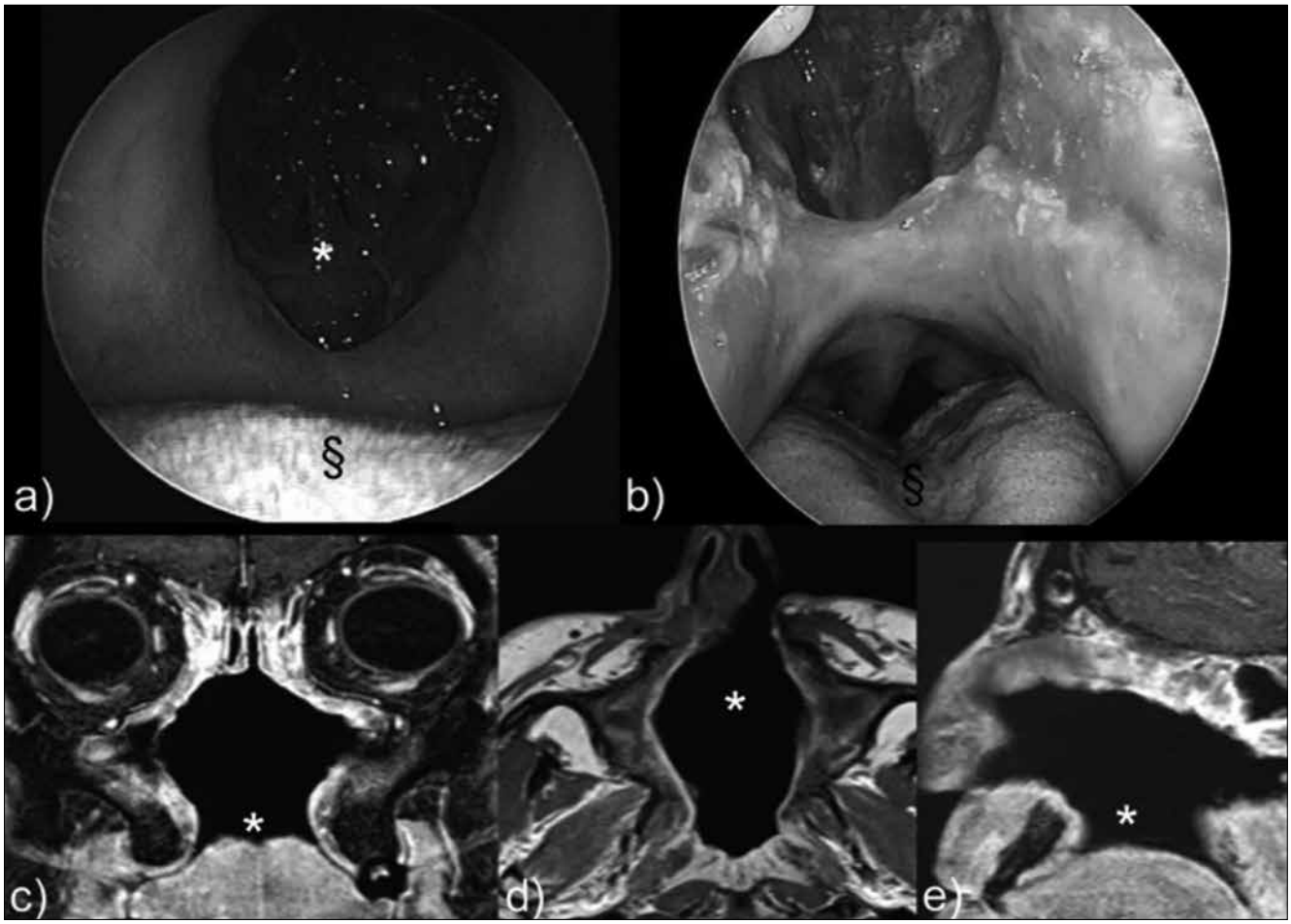


Fig. 1. a) Oral endoscopy (0° rigid fiberscope): large 4 cm palate perforation. **b)** Nasal endoscopy (0° rigid fiberscope): 4 cm hard palate perforation (§). **c)** MRI in the coronal plane shows destruction of the inferior, middle, and superior turbinates on both sides, partial reabsorption of the left medial wall, and palate perforation. **d)** Destruction of the central nasal septum and lateral nasal structures (middle turbinate) is shown by MRI axial study. **e)** Palate perforation (*) is shown in the sagittal plane.

studies, respectively, differentiation between CIMDL and limited ENT GPA may pose several problems. Considering the histological features of CIMDL reported in the literature [5] and in our experience, we frequently found the presence of vascular changes including microabscesses in the venule wall and leukocytoclastic vasculitis, which have been proposed as characteristic features of GPA [8-10]. Consequently, the histologic changes observed in a large proportion of biopsies from patients with CIMDL might be misinterpreted as "consistent with GPA" [8]. Only extravascular changes consisting in giant cells and microscopic foci of deeply located necrosis may be diagnostic of GPA [5-11].

However, as described in a previous study [12], in situ TUNEL assay on biopsy specimens can be useful to demonstrate apoptotic cells because they are highly characteristic features of CIMDL. If histological analysis is non-diagnostic, the next step is ANCA determination, although ANCA test positivity is not always discriminatory between CIMDL and GPA. Anti-neutrophilic cytoplasmic antibodies (ANCAs) directed against proteinase 3 (PR3) or myeloperoxidase (MPO) are sensitive and specific markers for GPA. However, instances of positive ANCA test results have been reported in an unexpectedly large proportion of patients with CIMDL [5]. In order to discriminate between CIMDL and GPA, Wiesner et al. made a detailed analysis of the ANCAs and found a high frequency (84%) of anti-human neutophil elastase (HNE) ANCAs in patients presenting with CIMDL. This finding allowed the authors to conclude that HNE ANCAs are discriminatory, whereas the presence of PR3 ANCAs is not. Consequently, in a clinical setting of necrotising inflammation of the upper respiratory tract, additional testing for HNE ANCAs may be useful in differentiating CIMDL from limited ENT GPA [7]. Unfortunately, this diagnostic method in not commonly available in routine practice. Differential diagnosis is difficult to reach in the case of HNE ANCA negativity, and in this case there are no discriminating elements.

To facilitate diagnosis of CIMDL and reduce the rate of misdiagnosis with other pathological conditions, we propose a diagnostic algorithm that takes into account the

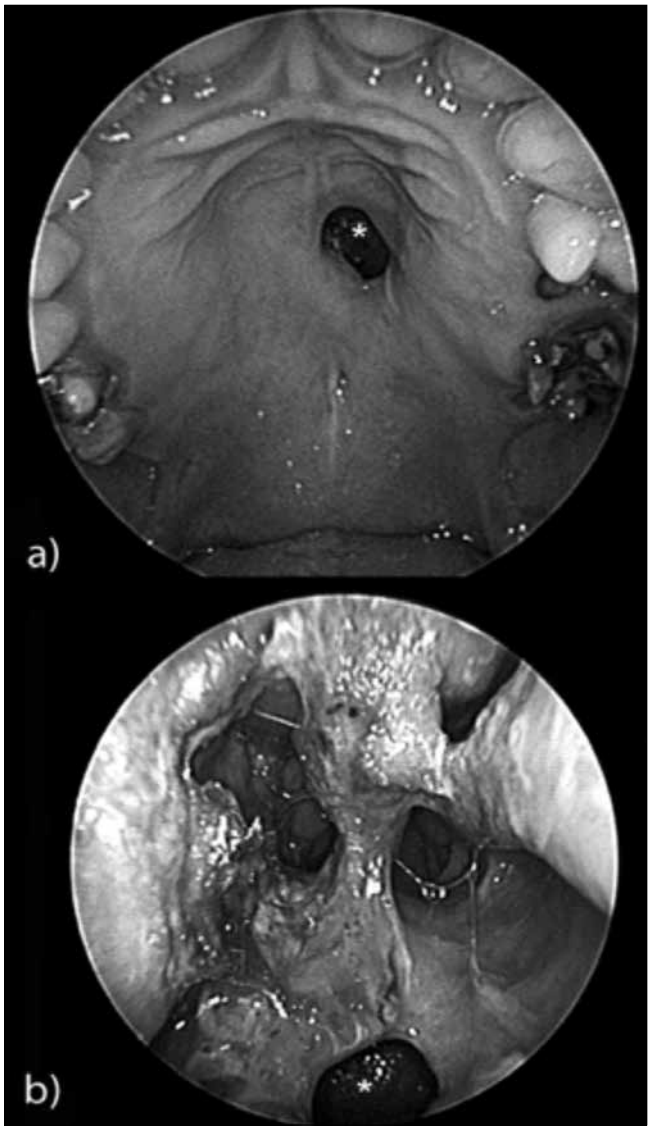


Fig. 2. a) Oral endoscopy (0° rigid fiberscope): a 1 cm hard palate perforation with regular margins (*). **b)** Nasal endoscopy (0° rigid fiberscope): typical nasal crusting in a cocaine abuser with 1 cm hard palate perforation (*).

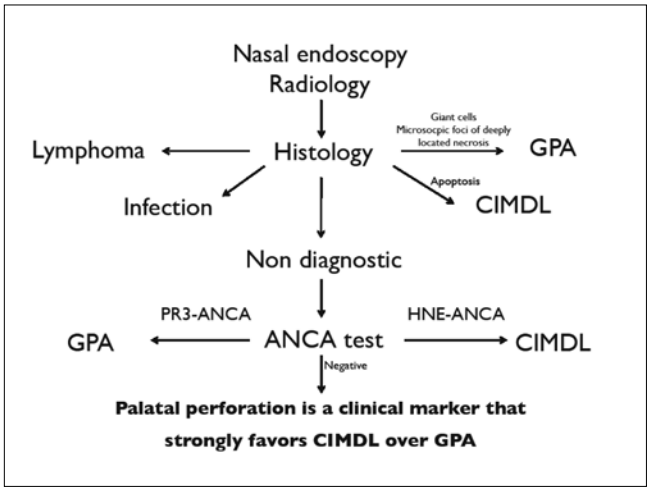
presence of palate perforation. This can help diagnostic choice when clinical doubt is focused on CIMDL and GPA (Fig. 3).

For this reason, we consider palate perforation to be an additional diagnostic element. In our experience, palate perforation is frequently associated with cocaine abuse [5], but we have never observed cases of palate perforation in patients with GPA [13].

From a review of the literature, palate perforation has been described in 73 CIMDL patients, while there are only 5 reports of subjects affected by GPA with palate perforation, for which a few comments are warranted.

Kasifoglu et al. [14] described the case of a 26-year-old woman admitted with nasal septum and palatal destruction. The authors reported indeterminate cANCA positivity and a histopathological diagnosis of GPA, but these elements were not exhaustive for definitive diagnosis because CIMDL could not be excluded. Moreover, the same authors defined palatal destruction as a rare condition in the course of GPA, citing three papers from literature [15-17] in which palatal perforation was not mentioned. Molloy et al. [18] did not present a published case, but indirectly describe their personal GPA experience with one case of palatal perforation in a letter. Manganaro et al. [19] imputed their case of soft palatal loss to GPA without ANCA test positivity or biopsy, and therefore with a debatable diagnosis. Aries et al. [20] presented a case of palatal perforation without biopsy because it was refused by the patient: the final diagnosis relied on non-histological criteria for GPA. In contrast, Sciascia et al. [21] presented the case of a 49-year-old woman with perforation of the midline and no other signs of systemic disease. A biopsy revealed a chronic inflammatory process with giant cells, pathognomonic of GPA.

Fig. 3. Diagnostic algorithm for CIMDL.



Recently, a proportion of idiopathic cases of midline destructive lesion have been attributed to IgG4-related disease (IgG4-RD), a novel systemic fibro-inflammatory condition characterised by tumourous swelling of affected organs and serum IgG4 elevation [22 23]. IgG4-RD was shown to involve midline structures both in the form of mass-forming lesions and nasal or palatal erosions, thereby introducing an additional differential diagnosis to CIMDL. However, in contrast to GPA and CIMDL, the incidence of IgG4-RD is largely unknown and palatal perforation remains an anecdotal observation from a single centre case series that requires further confirmation. In addition, as we recently reported, IgG4-RD might be accurately differentiated from CIMDL thanks to specific histological hallmarks, such as storiform fibrosis, IgG4+ positive plasma cells, and obliterative phlebitis [24].

In conclusion, our experience and the present review of the literature demonstrate that palatal perforation is strongly suggestive of CIMDL and represents an impor-

tant diagnostic element that can enrich diagnostic workup between GPA and CIMDL.

Conclusions

In conclusion, the presence of palate perforation in patients with MDL and negative biopsy and negative ANCA test may represent a clinical marker that strongly favours CIMDL over GPA.

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Review of the literature

Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Becker- Hill (1988)								
Kuriloff and Kimmelman (1989)	29/F	Saddle nose deformity with nasal valve collapse, total necrosis of ns and turbinates. Crusting granulation tissue and exposed bone**. 4mm oronasal fistula.**	2-year history of several grams weekly.	Chronic inflammation without any evidence of vasculitis and granulomas.	-	Antibiotics. Saline irrigation Prosthesis.	-	-
Deutsch and Millard (1989)	24/ F	Collapsed nasal dorsum, 80% of ns was perforated, ulceration of superior **face of the palate**, the uvola was absent, ulceration of the posterior pharyngeal wall.	2 and 1/2 years daily.	No evidence of malignancy.	-	-	-	-
Mattson-Gates et al (1991)	28/ F	Collapsed nasal bridge, septal perforation and **hard palate perforation (1,5 x 1cm).**	4 years.	-	-	-	-	1 week
Sousa–Rowley (1994)								
Armstrong and Shikani (1996)	31/ F	Destruction of the entire cartilaginous and bony ns, lateral nasal wall. **Oro-nasal fistula (7mm).**	-	Acute and chronic inflammation with granulation tissue, eosinophils and necrotic debris, no evidence of foreign material granuloma or vasculitis. Stains for fungi and acid-fast bacteria were negative.	Weakly positive (1:40)	Intravenous antibiotics, extensive debridement.	Stable.	20 months.
Helie and Fournier (1997)	46/ F	Ns, complete destruction of the inferior and MTs, destruction of nlw, destruction of the ethmoid cells and partial dehiscence of right lamina papyracea. **Large hard palate perforation (2,8X1,5cm).**	Several gr/ week for 13 years.	Non specific inflammatory response.	Negative	Antibiotics and extensive debridement Surgical repair of oronasal fistula		6 months
Sastry (1997)	37/ F	Ns perforation **palatal defect.**	Longstanding history.	-	-	-	-	-

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follows.

Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Sittel and Eckel (1998)	36/M	Necrosis of the ns, inferior and MTs, lower ethmoidal cells. **1.5 cm destruction of the palate with loss of the uvola.**	Heavy cocaine abuse.	Necrosis and ulceration with sign of inflammation but no evidence of vasculitis or granulomatosis.	c-ANCA	Rehydration antibiotics and debridement	Deterioration: absence of the ns, inferior and MTs, lower ethmoidal cells as well as 1,5 cm destruction of the palate with loss of the uvula.	1 year
Gendeh BS et al. (1998)		progressive septal as well as palatal perforation.		no histologic evidence of Wegener's Granulomatosis	c-ANCA			
Villa (1999)	38/M	Saddle nose deformity, **Oro-nasal fistula** (10x12mm).	Several years.	Non-specific ulcer and chronic inflammation with some eosinophils.	_	Management of recurrent sinus infections and removable obturator for the fistula	_	_
Caravaca et all (1999)	40/M	Saddle nose, ns, inferior, MTs, **soft palate**	Several years.	Non-specific inflammation	_	_	_	_
Braverman et al. (1999)	45/F	Saddle nose, completely eroded ns, complete erosion of ITs, erosion of the nlw, erosion of the anterior sphenoid wall and of the sphenoid floor, **1-cm oronasal fistula in the mid portion of the hard palate**, clefting of soft palate to the left of the uvula	Longstanding history	_	_	Rotation flap to close oronasal fistula and posterior soft palate cleft. After flap had broken down, a removable acrylic appliance was applied	_	_
Cottrell et al.(1999)	33/W	Hard palate perforation, nasal septal perforation	5 years	Chronic inflammation of the squamous epithelium without granulomas or vasculitis		Palate obturator	-	-
Tsoukalas et al.(2000)		Hard palate perforation	> 10 years					
Lancaster J (2000)	33/F	palatal necrosis, extensive necrosis also involved the cartilaginous and bony septum and paranasal sinuses						

continues

follows.

Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Talbott JF et al. (2001)	56/M	progressive destruction of his hard palate, septum, nasal cartilage, and soft palate that had been caused by chronic cocaine inhalation.		Biopsy of the bony septum revealed acute osteomyelitis and an extensive overgrowth of bacteria and Actinomyces-like organisms. There was no evidence of granuloma or neoplasm.		ampicillin/ sulbactam for 6 weeks, followed by lifetime oral amoxicillin. When there was no further evidence that destruction was progressing, the patient underwent nasal reconstruction with a cranial bone graft.		
Gertner E. et al. (2002)	53/M	destruction of septum, nasal cartilage with large oronasal fistula in his palate	30 years	Acute and chronic inflammation, necrosis	c-ANCA neg p-ANCA pos	Surgical debridement		
Marì A (2002)	37/M	Oronasal communication and defect of the labial philtrum, columella, vomer, septal cartilage	1 year	Unspecific ulceration and chronic inflammation	c-ANCA neg	Palatal obturator and lavages with saline solution	Program of dehabituation with stopping use of cocaine after 6 months	--
Marì A (2002)	35/W	Large oronasal communication, loss of vomer and nasal cartilage, saddle nose deformity	Several years	Chronic inflammation with reactive epithelial hyperplasia	c-ANCA neg	Palatal obturator and lavages with saline solution	She stopped use of cocaine and was treated with an anterior based tongue flap	--
Marì A (2002)	30/W	Oronasal communication, loss of vomer and nasal cartilage.	4 years	Chronic unspecific inflammation	--	Palatal obturator	She did not cease cocaine inhalation	--
Seyer BA (2002)	50/F	Bilateral collapse of nasal ala, complete loss of palatine process of maxilla, walls of maxillary sinus, turbinates, nasal septum and ethmoid sinus **vericare**	Several years	Acute and chronic inflammation, necrosis, squamous metaplasia of minor glands, no vasculitis, no evidence of malignant disease	c-ANCA positive	Debridement, oral antibiotics. Lost to follow-up before definitive surgical treatment	--	--
Ronda (2002)	40/M							
Smith et al (2002)	47/W	Hard palate defect, nasal septal perforation	14 years	Chronic granulomatosis and areas of necrosis in the tissue	c-ANCA neg	--	--	--

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follows.

Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Monasterio L (2003)	64/ M	Hypernasal voice, liquid and food through the nose 6 X 7 mm fistula of the posterior portion of the hard palate. Nasal septal perforation but no saddle nose deformity.	--	--	--	Surgical repair: palatal defect was resolved with standard cleft palate surgery technique (bipedicle mucoperiosteum flap)	No evidence of fistula	1 year
Trimarchi et al (2003)	41/W	Pain in the suborbital area with swelling and erythema of surrounding tissue; nasale septal perforation, total destruction of inferior, middle and superior turbinate and hard-soft palate				Antibiotics, steroids, radiotherapy, cyclophosphamide, azatioprine	Progressive rapid deterioration with orbit involvement	9 years
	25/F	Oronasal reflux, rhinolalia. nasal septal perforation, total destruction of inferior, middle and superior turbinate and hard-soft palate				Antibiotics, steroids, cyclophosphamide, azatioprine	No progression	8 years
	45/M	Nasal obstruction, nasal pain, anosmia nasal septal perforation, total destruction of inferior, middle and superior turbinate and soft palate				Antibiotics, saline solution irrigation, local debridement	Progressive deterioration with severe enlargement of the soft palate	5 years
	40 /F	Nasal obstruction, anosmia, posterior open rhinolalia nasal septal perforation, total destruction of inferior, middle and hard palate				Antibiotics, saline solution irrigation, local debridement	Hard palate perforation	5 years
	66/M	Nasal obstruction, hyposmia, epistaxis Hard palate perforation				Antibiotics, saline solution irrigation, local debridement	Hard palate perforation	4years
	40/M	Nasal ostruction, headache nasal septal perforation, total destruction of inferior, middle and hard palate				Antibiotics, saline solution irrigation, local debridement	Enlargement of hard palate perforation	6 months
Ladner et al (2004)	37/W	Right wing of the right ala nasi, soft palate and nearly all of the lateronasal wall	Several years			Surgical repair with fasciocutaneous radial forearm free flap		
Westreich and Lawson (2004)		Oronasal/ oroantral fistulas		Chronic inflammation				
Westreich and Lawson (2004)		Oronasal/ oroantral fistulas		Chronic inflammation				

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follows.

Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Westreich and Lawson (2004)		Oronasal/ oroantral fistulas		Chronic inflammation				
Westreich and Lawson (2004)		Oronasal/ oroantral fistulas		Chronic inflammation				
Westreich and Lawson (2004)		Oronasal/ oroantral fistulas		Chronic inflammation				
Bains and Hosseini-Ardehali (2005)	36/M	Nasal reflux for liquid and food Rhinolalia Presence of a hole in his hard palate	Several years	Chronic inflammation		Acrylic partial palat obturator		1years
Goodger NM (2005)	43/F	Oro-nasal communication (3 X 1.5 cm) couplet with destruction of nasal septum and lateral wall of nose	5 years	Microbiology, histopathology and serological examination showed only necrotic bone and soft tissue with no other pathology	--	Areas of necrosis were debrided; after 6 months definitive reconstruction was undertaken using an anteriorly base lareral tongue flap	Three weeks later the pedicle was divided once the flap was vascularized from the periphery	--
Jewers WM (2005)	31/M	Oro-nasal fistula involving the hard palate (8X11 mm) conditioning rhinolalia	-	Focal inflammatory changes;the inflammatory infiltrate was characterised by a dense plasmacytic infiltrate with scattered eosinophils	--	Unsuccessful surgical repair of the fistula	acrylic palatal obturator was placed in the palatal defect	-
Padilla-Rosas M (2006)	48/F	Septal perforation and asymptomatic hard palate ulcer 15 X 17 mm without inflammation signs **vericare**	1 year	Biopsy was performed revealing necrotic areas with chronic inflammatory infiltration and squamous metaplasia in several minor salivary glands	--	Palatine obturator	--	--
Simsek S (2006)	34/M	Septal perforation, saddle nose deformity and hard palate perforation	Several years	Microscopy of the nasal mucosa showed a chronic active necrotizing inflammation without a clearly granulomatous aspect	c-ANCA	Sulphametoxa-zole, trimetroprim and oral corticos-teroids	Obturator was placed in the palatal defect	--
Simsek S (2006)	30/M	Septal perforation and hard palate fistula	--	-----	p-ANCA	Sulphametoxa-zole, trimetroprim	--	--

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Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Brusati (2007)	46/F	Hard and soft palate defect, nasal anterior cranial base defect (direct communication brain –mouth) Encephalocele associated with meningitis	Several years	-----	--	Multiple surgical approach with free flap reconstruction	--	--
Harkes ML et al. (2007)	56/M	Oronasal fistula	--	--	--	--	--	--
Di Cosola M. (2007)	1° pz age 29-46	intranasal destruction of the vomer and nasal septum cartilage preceded the hard palate perforation	Several years (7,5 years)	Necrotic and granulation tissue along the margins of the palatal defect	---	Fascio-cutaneous radial flap forearm free flap was planned to reconstruct the hard palate defect	New palatal perforation due to restart of substance abuse	4,5 years
Di Cosola M. (2007)	2° pz age 29-46	intranasal destruction of the vomer and nasal septum cartilage preceded the hard palate perforation	Several years (7,5 years)	Necrotic and granulation tissue along the margins of the palatal defect	---	Fascio-cutaneous radial flap forearm free flap was planned to reconstruct the hard palate defect	New palatal perforation due to restart of substance abuse	2 years
Di Cosola M. (2007)	3° pz age 29-46	intranasal destruction of the vomer and nasal septum cartilage preceded the hard palate perforation	Several years (7,5 years)	Necrotic and granulation tissue along the margins of the palatal defect	---	Local three plane closure: nasal mucosal flap, tunnelized buccal fat pad coming from the cheek and a rotational oral flap	Improvement in speech intelligibility, voice recording interpretation and swallow videofluoroscopy (no restart of substance abuse)	2 years
Di Cosola M. (2007)	4° pz age 29-46	intranasal destruction of the vomer and nasal septum cartilage preceded the hard palate perforation	Several years (7,5 years)	Necrotic and granulation tissue along the margins of the palatal defect	---	Fascio-cutaneous free flap (the author introduces a personal modification of the Marshall's technique)	Improvement in speech intelligibility, voice recording interpretation and swallow videofluoroscopy (no restart of substance abuse)	3 years
Di Cosola M. (2007)	5° pz age 29-46	intranasal destruction of the vomer and nasal septum cartilage preceded the soft palate perforation	Several years (7,5 years)	Necrotic and granulation tissue along the margins of the palatal defect	---	Trilobe-shaped radial forearm free flap was planned to reconstruct the soft palate defect	Improvement in speech intelligibility, voice recording interpretation and swallow videofluoroscopy (no restart of substance abuse)	3 years

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follows.

Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Di Cosola M. (2007)	6° pz age 29-46	intranasal destruction of the vomer and nasal septum cartilage preceded the hard and soft palate perforation	Several years (7,5 years)	Necrotic and granulation tissue along the margins of the palatal defect	---	Trilobe-shaped radial forearm free flap was planned to reconstruct the hard and soft palate defect	Improvement in speech intelligibility, voice recording interpretation and swallow videofluoroscopy (no restart of substance abuse)	4 years
Lypka MA, Urata MM (2007)	25/M	Midline palate perforation, large nasal perforation	5 years	---	---	---	---	---
Cohen et al. (2008)	54/M	Mieline hard palate perforation 6x6 mm.	23 years	Large septal perforation.	---	Local mucoperiostieal flap	---	---
Cintra HL et al (2008)	25/F	Hard palate perforation 4x7 cm.	8 years	---	Refused ANCA test	Bipedicled mucoperiostium flap	Speech improvement	4 months
Cintra HL et al (2008)	42/F	Hard palate perforation 4x6 cm.	4 years	---	c-ANCA +/-	Bilateral monopedicled mucoperiotium flap	Speech improvement	4 years
Fava M et al. (2008)		ulcerated lesion in the palate of a cocaine-using patient						
Tartaro G et al. (2008)		oronasal fistula involving hard palate and the right supero-lateral vestible induced by prolonged cocaine snort						
Hofstede T.M. (2010)	48/M	Erosion of palate, nasal septum, inferior nasal turbinates	Multiple times daily for months	Acute and chronic inflammation with evidence of Staphylococcus aureus infection	---	Prosthetic management of palatal defect	Partial restoration of speech and swallowing	3 years
Silvestre FJ et al.(2011)	34/F	Hard palate perforation and oronasal communication Lesion size 12 X 8 mm Speech and swallowing difficulties	9 years	----	-	--	-	-
Silvestre FJ et al.(2011)	37/M	Hard palate perforation and oronasal communication Lesion size 22 X 18 mm Speech and eating difficulties	17 years	Epithelial hyperplasia and basal layer chronic inflammatory infiltrate No signs of vasculitis	-	Failure of surgical approach	-	

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Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Silvestre FJ et al.(2011)	41/F	Hard palate perforation and oronasal communication Lesion size 37 X 19 mm Pain and overinfection	7 years	chronic inflammatory infiltrate No signs of vasculitis	-	--	-	
Silvestre FJ et al.(2011)	44/M	Hard palate perforation and oronasal communication Lesion size 35 X 16 mm Speech and eating difficulties	9 years	--	--	--	-	-
Stahenlin L et al. (2012)	43/F	Nasal septum and palate perforation Nasal obstruction and nasal voice and rhinorrhea	5 years	chronic inflammation with granulation tissue no evidence of vasculitis	P Anca test +	---	---	--
Van der Peol NA et al. (2013)	41/M	Extensive deformities of and tissue defect of the nose and palate	-	-	-	Surgical approach	Failure and relapse of defect due to persistent cocaine abuse	-
Colletti G et al. (2013)	41/M	Collapse nose, absence of nasal septum Wide oronasal fistula 30 X 20 mm	10 years	-	-	Fistula closure with radial forearm free flap	Good outcome	12 months
Colletti G et al. (2013)	39/W	Bilateral collapse of the nasal tip, dorsum and alae. Palatal fistula present	9 years	-	-	Fistula closure with radial forearm free flap	Good outcome	18 months
Colletti G et al. (2013)	37/W	Fistula in hard palate, tatl destruction of the nasal septum. Oronasal regurgitation of both solid and liquids	10 years	-	-	Local debridment for persistent abusive habits	-	-
Colletti G et al. (2013)	35/W	Saddle nose deformity with a wide oronasal fistula; oronasal regurgitation of both solid and liquids	5 years	-	-	Palate reconstruction with radial forearm free flap	Good outcome	12 months
Brembilla C et al (2014)	44/M	Septal and hard palate perforation. Nasal obstruction, epistaxis, nasal reflux, neck pain	25 years	Granulation tissue with mixed inflammatory infiltrates	cAnca test neg	Local debridment. regular saline douches Antibiotic therapy Craniovertebral fixation	-	-

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follows.

Author(s)	Sex/ Age	Clinical and radiological findings	Cocaine history	Pathology	ANCA	Therapy	Outcome	Follow-up (yr)
Rilo B et al. (2014)	31/W	Oronasal fistula 15 X15 mm in the posterior hard palate. Hypernasal speech, nasal obstruction, anosmia. Oronasal regurgitation	7 years	-	-	unsuccessful. surgical reconstruction. Resin obturator	-	-
Boulagnon C et al. (2015)	42/M	Hard palate perforation	-	-	-	-	-	-
Pekala et al. (2015)	24/M	Absence of nasal septum, heavy crusting; erosive process extended through the hard palate. Nasal congestion with rhinorrhoea	2 years	Inflammatory infiltrate with necrosis, fungal hyphae	-	Amphotericin B an voriconazole. Palatal Obturator	-	-
Trimarchi et al (2016)	39/M	Oronasal communication	persistent abuse	-	-	Nasal septal button for the sealing o palatal perforation	-	-