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Cocaine-Induced Midline Destructive Lesions

Clinical, Radiographic, Histopathologic, and Serologic Features and their Differentiation from Wegener Granulomatosis

MATTEO TRIMARCHI, GINA GREGORINI, FABIO FACCHETTI, MARIA LAURA MORASSI, CINZIA MANFREDINI, ROBERTO MAROLDI, PIERO NICOLAI, KIMBERLY A. RUSSELL, THOMAS J. MCDONALD, AND ULRICH SPECKS

Introduction

Habitual nasal insufflation of pulverized cocaine may cause mucosal lesions. Mild changes cause nasal stuffiness, headache, or hyposmia. If cocaine use becomes chronic and compulsive, progressive damage of the mucosa and perichondrium leads to ischemic necrosis of the septal cartilage and perforation of the nasal septum. Occasionally, cocaine-induced lesions cause extensive destruction of the osteocartilaginous structures of the nose, sinuses, and palate that mimics the clinical picture of other diseases associated with necrotizing midfacial lesions (1, 4, 17, 20, 31, 38, 43, 49, 58, 62, 63, 66, 74). The mucosal damage induced by cocaine is multifactorial. The vasoconstrictive effect of the drug is thought to be the most important factor (8, 17, 20, 38). However, the irritant effect of adulterants of the drug, the traumatic effect on the mucosa caused by cocaine crystals insufflated at high velocity, and recurrent nasal infections all seem to contribute to chronic tissue destruction (20, 38). Progressive nasal obstruction, epistaxis with crusting, and ulceration of the nasal mucosa with or without septal perforation are also characteristic manifestations of nasal involvement by Wegener granulomatosis (WG). The differentiation of cocaine-induced midline destructive lesions (CIMDL) and limited WG may be difficult, particularly if the patients do not readily admit to their substance abuse.

Antineutrophilic cytoplasmic antibodies (ANCA) directed against proteinase 3 (PR3) or myeloperoxidase (MPO) are sensitive and specific markers for the idiopathic small vessel vasculitides including WG (30). It is generally believed that the presence of a positive ANCA test result with either of the 2 antigen specificities facilitates the differential diagnosis of WG. However, instances of positive ANCA test results have been reported in patients with lesions attributed to cocaine abuse (4, 29). We found positive ANCA test results in an unexpectedly large proportion of patients with CIMDL. In several instances their lesions were clinically indistinguishable from WG limited to the upper respiratory tract (28). This seems to limit the usefulness of routine ANCA testing for the unequivocal differentiation of cocaine-induced nasal lesions from limited WG.

We performed the present study to identify clinical, radiographic, and histopathologic features that allow the distinction of patients with severe CIMDL from those with WG and to further characterize their ANCA.

Patients and Methods

Patients

Between January 1991 and December 1999, 18 cocaine abusers with midline destructive lesions were evaluated in the Department of Otolaryngology of the University of Brescia, Italy (Table 1). The patients ranged in age from 22 to 66 years (median, 37 yr). Ten were men and 8 women. The follow-up period ranged from 12 to 108 months (median, 34 mo). At the time of first observation, all patients except 1 admitted to cocaine use. In 7 patients reliable information on abuse duration and dose could not be obtained, 2 patients had a history of abuse with an undetermined dose lasting 6 and 8 years, respectively. One patient had been using 1–3 g per week irregularly. The remaining 8 patients had been using cocaine for 2–30 years, at a dose ranging from 1 to 15 g per week.

The control population consisted of all 21 consecutive WG patients who underwent a nasal biopsy in the Department of Otolaryngology of the University of Brescia during the same time frame (see Table 1). Patients' ages ranged from 30 to 64 years (median, 45 yr). Nine were men and 12 women. The follow-up period

From Departments of Otorhinolaryngology (MT, PN), Nephrology (GG), Pathology (FF, LM, CM), Radiology (RM), University of Brescia, Italy; and Thoracic Diseases Research Unit and Division of Pulmonary and Critical Care Medicine (KAR, US), Department of Otolaryngology (TJM), Mayo Clinic and Foundation, Rochester, Minnesota, USA.

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Address reprint requests to: Gina Gregorini, MD, Department of Nephrology, Spedali Civili, Piazza Spedali Civili 1, 25123 Brescia, Italy. Fax: 030 3995012; e-mail: dotgina@mail.phoenix.it.

TABLE 1. Clinical features and laboratory values at presentation of patients with CIMDL and WG

	CIMDL (n = 18)	WG (n = 21)	p value
Male/female	10/8	9/12	0.037
Age (yr)	35 ± 10	45 ± 14	0.018
Fever	0	13	
Weight loss	0	7	
Arthralgia/arthritis	0	7	
Myalgia/myositis	0	5	
Facial pain	3	5	
Ear involvement	0	7	
Orbital pseudotumor	0*	2	
Subglottic stenosis	0	6	
Bronchial involvement	0	4	
Lung involvement	0†	12	
Skin involvement	0	4	
Multineuritis-cranial nerves	0	7	
RBC × 1,000/mL	4,665 ± 474	3,914 ± 814	0.002
Hemoglobin (g/dL)	14.2 ± 2.0	11.1 ± 2.1	0.000
WBC /mL	10,305 ± 2,868	10,690 ± 4,872	0.776
Platelets × 1,000/mL	333 ± 69	440 ± 193	0.037
CRP (mg/L)	12.2 ± 12	79.4 ± 73.7	0.002
ESR (mm/hr)	31 ± 25	66 ± 41	0.009
Total protein (g/dL)	7.6 ± 0.6	6.6 ± 0.6	0.000
Albumin (g/dL)	4.1 ± 0.6	3.4 ± 0.774	0.003
Alpha2 globulin (%)	11.2 ± 2.7	12.9 ± 3.7	0.064
Gammaglobulin	18.5 ± 5.1	19.5 ± 3.9	0.538
ANA positive	3/16	6/18	
RF positive	0/8	5/11	
Low complement	0/9	0/18	
Serum creatinine	0.9 ± 0.18	1.01 + 0.4	0.302
Microhematuria	2/17‡	13/21§	
Proteinuria	2/17‡	13/21§	

*During follow-up, 2 patients developed orbital pseudotumor with diplopia due to infection propagating from the nose that promptly responded to antibiotic treatment.

†During follow-up, 1 patient developed a *Staphylococcus aureus* lung abscess which resolved rapidly with antibiotic treatment.

‡Only trace in different patients.

§Ranging from trace to +3 in the same patients.

ranged from 13 to 108 months (median, 52 mo). Nineteen patients were evaluated at the time of first diagnosis, 2 at the time of their first relapse. Five WG patients had generalized disease with renal involvement, 3 had limited disease involving only the nasal and tracheal mucosa. The remaining 13 patients had lung involvement and other systemic symptoms but no kidney involvement. All patients had biopsy-proven WG or satisfied the Chapel Hill Consensus Conference definition (35) of the disease.

Clinical and laboratory evaluations

Physical examination included inspection of the face, oral cavity, and oropharynx; inspection of the nasal cavities and nasopharynx using 0° and 30° rigid telescopes, 4 mm in diameter, and the flexible fiberscope. Multiple biopsies and samples for bacterial and fungal cultures were taken under endoscopic guidance. To monitor the clinical course of the disease, digital images of the relevant endoscopic features were archived.

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete and differential blood counts, liver and kidney function tests, urinalysis and microscopy, and serology for hepatitis virus B and C and human immunodefiency virus (HIV), were performed in every patient. In addition, antinuclear antibodies (ANA), rheumatoid factor (RF), and complement levels were determined in most patients.

ANCA determination

All sera from CIMDL and WG patients were tested for ANCA in 3 different laboratories. ANCA tests were first performed at the time of the patients' clinical evaluation in the laboratory of the Department of Clinical Immunology of Spedali Civili, University of Brescia, Italy. Sera were analyzed by indirect immunofluorescence microscopy (IIF) on ethanol-fixed blood donor neutrophils following the standard procedure delineated at the first ANCA workshop (77). Sera were further tested by enzyme-linked immunosorbent assays (ELISA) for the presence of antibodies reacting with PR3 (PR3-ANCA) and MPO (MPO-ANCA). PR3, purified as previously described (65), and MPO obtained from a commercial source (Calbiochem Biosciences, Inc. La Jolla, CA) served as antigens in the assays.

Aliquots of the sera were subsequently analyzed at the Mayo Clinic (Rochester, MN) by IIF and ELISA for MPO-ANCA following a standardized test algorithm (68). For some of the WG patients only convalescent sera were available for testing at Mayo (see Table 2). In addition, the sera were analyzed in the research laboratory of 1 of the authors (US) by IIF for PR3-ANCA and human leukocyte elastase (HLE)-ANCA using ethanol-fixed HMC-1 cells that expressed recombinant PR3 (rPR3) or HLE (rHLE) (56, 69). Furthermore, the sera were tested for PR3-ANCA by capture-ELISA using purified neutrophil PR3 (Athens Research, Athens, GA) as target antigen (71). IIF results obtained using neutrophils were expressed qualitatively as showing characteristic cytoplasmic staining (C-ANCA) or perinuclear staining (P-ANCA). IIF results using HMC-1 cells expressing rPR3 or rHLE were reported as positive when characteristic IIF staining was detected at a serum dilution of 1:4 or higher that was not detectable on sham-transfected HMC-1 (HMC-1/VEC) control cells (69). Solid-phase assay results were expressed in arbitrary units.

Imaging studies

Sixteen of the 18 CIMDL patients underwent cross-sectional imaging. A total of 24 examinations were evaluated: 7 computed tomography (CT) studies in 5 patients, and 17 magnetic resonance (MR) studies in 11 patients. Four patients had more than 1 imaging study (range, 2–5). Sixteen of the 21 WG patients were evaluated by cross-sectional imaging: 2 by CT and 14 by MR.

The imaging studies were obtained shortly after the endoscopic examination in all patients (range, 2–25 d). Of the CIMDL patients, 4 patients had additional examinations (n = 8) during the follow-up (range, 7–52 mo). All MR studies were performed at the Department of Radiology of the University of Brescia using superconductive equipment (Siemens Magnetom SP 1.5 T, Symphony 1.5 T). In all MR studies, spin echo or turbo spin echo T2 sequences were acquired along with enhanced T1 sequences. All CT examinations were performed without contrast enhancement. Two of 5 CT studies were performed at the Department of Radiology, the others at different hospitals. All imaging studies were reviewed by 1 of the authors (RM).

We analyzed the degree of septal destruction, that is, its area, obtained by multiplying the maximum diameters of the eroded

septum, erosion of adjacent nasal structures (inferior, middle, superior turbinates), lateral nasal wall (medial antral wall, lamina papyracea) and floor of the nasal cavity (hard and soft palate). A score was obtained by assigning 1 point for each single structure involved. We evaluated abnormal changes of signal intensity of the mucosa on plain and enhanced MR sequences. In addition, we evaluated changes in size and signal of Waldeyer ring sites and abnormalities of the middle ear, and compared imaging studies obtained at the time of the first endoscopic examination. Follow-up studies were considered separately.

Histopathologic evaluation

A total of 44 mucosal biopsies from nasal cavities and paranasal sinuses were evaluated from the 18 CIMDL patients. Five patients had more than 1 biopsy (range, 2–16). Sections were stained with hematoxylin-eosin. Orcein staining was used to evaluate elastic fibers, and periodic-acid Schiff and Ziehl-Neelsen stains were used to identify fungi and mycobacteria, respectively. Polarizing filters were used to identify birefringent foreign material. Additional sections were immunostained for lymphoid pan-B-cell, CD20; pan-T-cell, CD3; Natural Killer (NK) cell, CD56 (Bio-SPA, Milan, Italy); and nonlymphoid, pan-macrophage, CD68 leukocyte-associated antigens. Stains for EBV-associated latent membrane protein 1 and RNA were performed using immunohistochemistry (anti-LMP1) and in situ hybridization (EBER-1,2), respectively. Twenty-nine nasal biopsies were obtained from 21 patients with WG and evaluated in the same fashion. (Unless otherwise indicated, all antibodies used were purchased from Dako, Milan, Italy.)

Statistical analysis

Quantitative variable analysis was performed using the nonpaired Student t-test. The qualitative histopathologic variables between the 2 groups were compared using the Fisher exact test. The radiologic variables between the 2 groups were compared using the chi-square test and the Pearson correlation coefficient. For all comparisons, p values of 0.05 or less were considered significant.

Results

Clinical and laboratory findings

All patients with CIMDL sought an otolaryngologic consultation because of longstanding symptoms including nasal obstruction, epistaxis, and severe facial pain. The most common findings at the first visit were diffuse necrotizing ulcerative lesions, extensive crusting, and septal perforation. Destruction of the septum and inferior turbinates was invariably found in all patients. In more severe cases it extended to the middle and superior turbinates and the lateral wall of the nose. The latter was entirely absorbed in 3 patients. Hard and soft palate perforations were present at initial presentation in 2 patients and became evident during follow-up in 3 additional patients (Figure 1). The lesions gave rise to dysphagia and nasal reflux, and substantially affected the patients' quality of life. An example of progressive destruction of the midline structures is shown in (Figure 2).

None of the CIMDL patients complained of symptoms suggesting ear, orbit, or lung involvement at initial presentation. During the course of the disease, 2 patients with severe destruction developed acute orbital symptoms caused by propagating infections associated with pseudotumor, proptosis, and diplopia. One patient developed a *Staphylococcus aureus* lung abscess. All these lesions resolved rapidly with appropriate antibiotic therapy. At presentation, constitutional symptoms such as fever, malaise, weight loss, as well as arthralgia or myalgia were universally absent in this patient group, and none of the patients had any symptoms or laboratory findings that would indicate a systemic disease process.

The clinical presentation of patients with WG was different. The degree of nasal destruction was less severe than in patients with CIMDL, and signs of other organ involvement were present in most of the WG patients. All 21 patients presented with nasal crusting, but only 3 with a septal perforation. None of the WG patients had involvement of the turbinates, lateral nasal wall, or palate. A comparison of the affected sites is shown in Figure 3.

In patients with WG, nasal symptoms were usually only 1 of several complaints. Clinical evidence of involvement of sites other than nose and sinuses were detected in all patients. Systemic symptoms and alterations in the blood tests were absent in only 2 WG patients at the time of initial presentation. Both were women with subglottic stenosis as the only extranasal manifestation of the disease. All other patients had constitutional symptoms and arthralgia or myalgia. The lungs, ears, and cranial nerves were the other sites most frequently affected.

Laboratory abnormalities were significantly more frequent in WG than CIMDL patients. Among the 21 WG patients anemia of chronic disease was found in 16, elevation of white blood counts in 12, and of platelet counts in 10. Increased levels of CRP and ESR were detected in 15 and 14 of the WG patients, respectively. Of the 18 CIMDL patients, 2 had anemia, 5 had elevated white blood counts, and 2 had elevated platelet counts. Abnormal CRP and ESR values were found in 9 and 8 CIMDL patients, respectively, but the mean values were significantly lower than those found in WG patients (see Table 1). Microhematuria and proteinuria were present in 13 of 21 WG patients, even in the presence of normal serum creatinine values. Several WG patients also had ANA (6 of 18 tested) or RF (5 of 11 tested). All CIMDL patients had normal liver and renal function test results and tested negative for hepatitis B antigen, hepatitis C, and HIV antibodies.

Fifteen of 17 CIMDL patients tested at the initial visit had positive nasal cultures for *S. aureus*. Thirteen of 21 WG patients were on broad-spectrum antibiotics at the time of diagnosis and, therefore, were

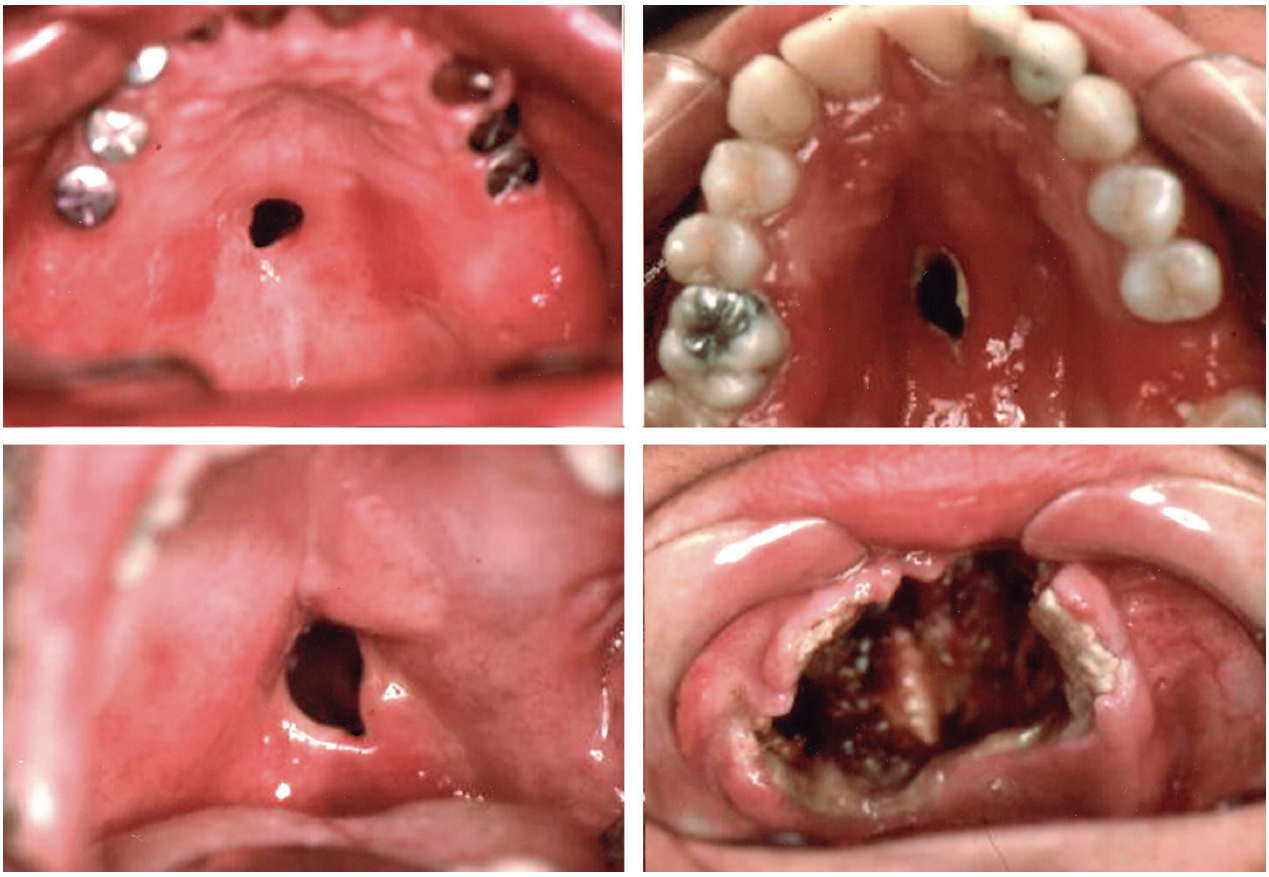

FIG. 1. Different examples of palate perforation in patients with cocaine-induced midline destructive lesions. The lesion can vary from a small defect to a large erosion involving the entire hard palate and extending to the alveolus.

not tested for *S. aureus*. Five of the remaining 7 WG patients not exposed to antibiotics had positive *S. aureus* nasal cultures.

ANCA results

All patients were tested for ANCA at initial presentation because WG was considered in the differential diagnosis of all necrotizing nasal lesions. A surprisingly large number of ANCA tests were positive in patients with CIMDL. The ANCA test results are summarized in Table 2. Only 5 of the 18 CIMDL patients were negative by all ANCA tests performed. In 8 patients, IIF was strongly positive for P-ANCA. All sera were negative for MPO-ANCA by ELISA. Three of the P-ANCA-positive sera reacted with rHLE, and 4 were positive in 1 or more of the tests performed to detect PR3-ANCA (direct ELISA, capture ELISA, or IIF on HMC-1/PR3 cells). Two of the P-ANCA-positive sera reacted with both HLE and PR3. Three of the P-ANCA-positive sera were negative for PR3-ANCA and HLE-ANCA.

Five patients with CIMDL had C-ANCA by IIF. All of them were positive for PR3-ANCA in at least 2 of the target antigen-specific assays. The IIF pattern of C-ANCA in the 5 patients was indistinguishable from that typically found in WG. IIF titers and direct ELISA assay units were as high as those encountered in WG patients. Two of the 5 C-ANCA-positive, PR3-ANCA-positive sera also reacted with HLE. Two others were completely negative in the PR3-ANCA capture ELISA although they displayed strong reactivity in the other PR3-ANCA assays.

Of the 21 WG patients, only 2 were ANCA negative (see Table 2). These were the patients with biopsy-proven disease affecting only the nose and subglottic area. Four patients had a P-ANCA pattern with corresponding positive MPO-ANCA ELISA test results, and 14 had a C-ANCA pattern with matching PR3-reactivity. Only 1 C-ANCA -positive WG patient re-

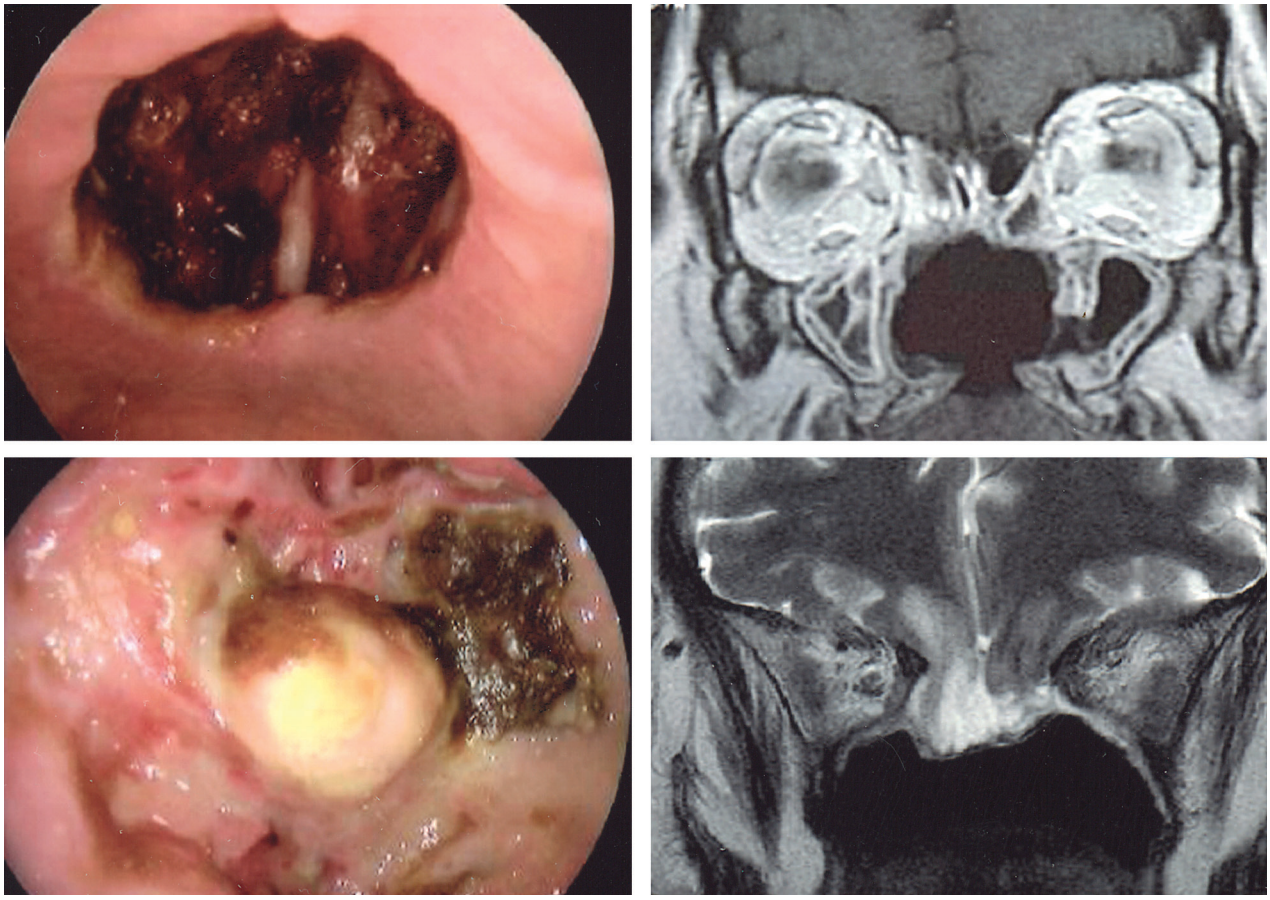

FIG. 2. Temporal progression of a midline destructive lesion in a patient with cocaine-induced midline destructive lesions over 3 years. In 1996, a large hard palate perforation was evident at inspection of the oral cavity (upper left panel). Magnetic resonance (MR) studies also demonstrated destruction of the inferior, middle, and superior turbinates on both sides and partial reabsorption of the left medial wall (upper right panel). By 1999, the lesion had progressed dramatically to destruction of the central part of the anterior skull base. The exposed dura and both frontal recesses are clearly visible in the endoscopic picture taken with a 70° scope (lower left panel). MR image shows the presence of a huge meningoencephalocele (lower right panel).

acted strongly with MPO but not PR3, a phenomenon that has been reported rarely (61). None of the ANCA-positive sera from WG patients reacted with HLE.

Taken together, the data indicate that routine ANCA testing alone does not allow the differentiation between cocaine-induced and WG-associated nasal lesions. However, more detailed analyses of ANCA specificities suggest that the ANCA immune response in patients with CIMDL differs from that usually encountered in WG patients. In WG it is much more target-antigen restricted.

Radiographic findings

To identify imaging characteristics that help to differentiate cocaine-induced lesions from WG-associated lesions, we analyzed the cross-sectional imaging studies obtained at initial presentation in patients of both groups (Table 3).

All CIMDL patients had septal perforations. Twelve of 16 (75%) had at least partial destruction of the inferior turbinate, which was bilateral in 9. Ten of the 16 cocaine abusers (62.5%) had partial or total destruction of at least 1 middle turbinate, which was bilateral in 5. Erosion of the superior turbinates was identified in 2 patients. The lateral nasal wall was eroded in 5 of the 16 (31.25%) patients. All had destruction of the medial maxillary wall; in 1 patient the erosion extended to the lamina papyracea. The floor of the nasal cavity was eroded in 4 of 16 patients (25%). In 1 of them the involvement extended to the soft palate.

In contrast, the imaging studies obtained at initial presentation in WG patients revealed a nasal septal perforation in only 2 of 16 (12.5%). The difference in

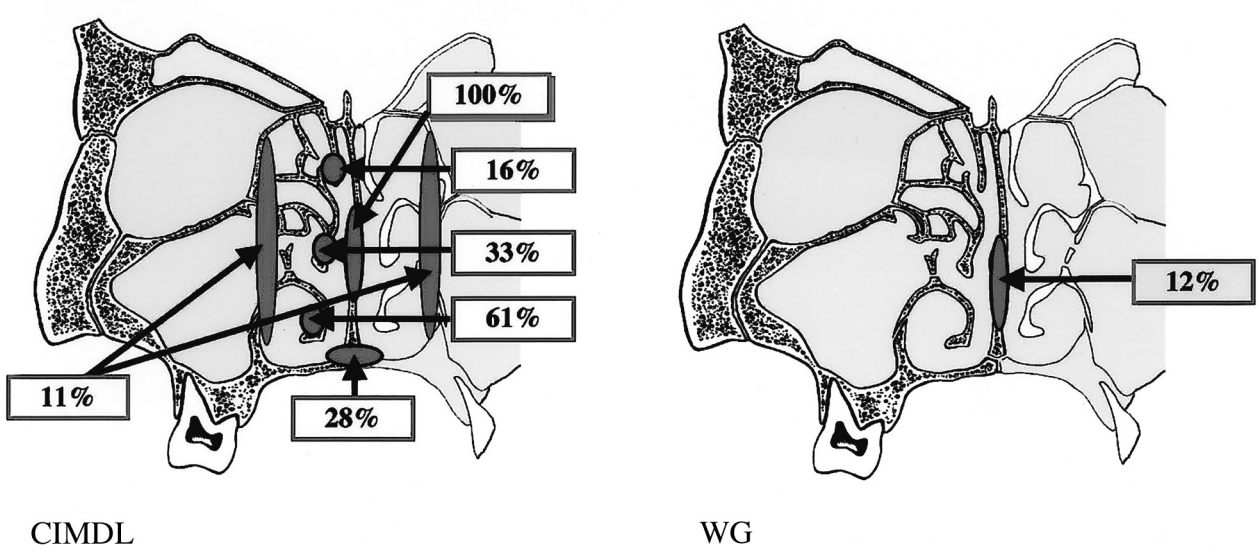

FIG. 3. Comparison of anatomic sites involved in cocaine-induced midline destructive lesions (CIMDL) and Wegener granulomatosis (WG) patients. The percentages indicate the proportion of patients of each group that had involvement of the indicated sites.

frequency of nasal septal perforation was statistically significant ($p < 0.0005$) with a positive predictive value of 88.9% for CIMDL. The involvement of a second nasal structure in addition to the nasal septum was discriminating between the 2 groups, as it was present in 75% of CIMDL patients but not in any of the WG patients.

Accordingly, the average radiographic score of affected structures was significantly higher in CIMDL patients (4.06; range, 1–10), compared with WG patients (0.13; range, 0–1; $p < 0.001$). A correlation was present between the extent of nasal septum perforation (mm^2) and the score. The correlation index was 0.803 in CIMDL patients ($p < 0.001$) and 0.708 in WG patients ($p = 0.002$). In addition, the occurrence of hard palate perforation in CIMDL patients was correlated with the destruction of bilateral inferior (Pearson 0.509; $p = 0.044$) or bilateral middle (Pearson 0.545; $p = 0.029$) turbinates.

In CIMDL patients, areas of an abnormal signal of nasal or paranasal mucosa such as hypointensity on T2 and reduced or nonhomogeneous enhancement were detected on 4 (36.36%) and 6 (54.54%) of the 11 MR scans, respectively. On the 14 MR scans obtained in WG patients, hypointensity on T2 and reduced or nonhomogeneous enhancement were present in 3 (21.4%) and 6 (42.8%) patients, respectively. Although MR abnormalities of the nasal mucosa were detected more frequently in CIMDL than in WG patients, the difference was not statistically significant. However, when only the mucosa of the central facial structures, that is, the nasal septum and the adjacent inferior and middle turbinates, was considered, reduced or nonhomogeneous enhancement was significantly more frequent in CIMDL than in WG patients (45.45% versus 16.66%; $p < 0.05$). Abnormal thickening of the mucosa of the paranasal sinuses was observed more frequently in WG (78.57%) than in CIMDL patients (54.54%), but the difference was not significant.

Significant enlargement of the palatine or pharyngeal tonsils was found on the imaging studies in 9 of 16 (56.25%) CIMDL patients. It was associated with small fluid collections within lymphatic tissue in most cases. Similar chronic inflammatory changes of the Waldeyer ring were significantly less common in WG patients ($n = 2$, 12.5%; $p < 0.05$).

Radiographic signs of otitis media were detected in only 1 CIMDL patient but in 5 WG patients (31.25%). All had different degrees of hearing impairment. In 1 of the WG patients, enhanced tissue within the middle ear was detected which turned out to be granulomatous tissue causing destruction of the ossicle chain. The difference of radiographic middle ear abnormalities did not reach statistical significance.

Follow-up imaging studies were obtained in 4 of the CIMDL patients. All of them admitted to continued cocaine abuse. All showed progressive erosion of nasal structures. In 1 patient there was progressive "centrifugal" involvement of the lateral nasal walls and floor with eventual destruction of the entire framework and complete erosion of the hard and soft palate. The central floor of the anterior skull base was also eroded (see Figure 2).

TABLE 2. ANCA test results in 18 patients with CIMDL and 21 patients with nasal destructive lesions caused by WG*

Patient ID	ANCA-IIF (Brescia/Mayo)	MPO-ANCA ELISA (Brescia/Mayo)†	PR3-ANCA ELISA (Brescia)‡	PR3-ANCA Capture ELISA (Mayo)§	HMC-1/ PR3-IIF (Mayo)	HMC-1/ HLE-IIF (Mayo)
			CIMDL			
CIMDL 1	−/−	−/−	−	−	−	−
CIMDL 2	−/−	−/−	−	−	−	−
CIMDL 3	−/−	−/−	−	−	−	−
CIMDL 4	−/−	−/−	−	−	−	−
CIMDL 5	−/−	−/−	−	−	−	−
CIMDL 6	P-ANCA	−/−	−	−	−	−
CIMDL 7	P-ANCA	−/−	−	−	−	−
CIMDL 8	P-ANCA	−/−	−	−	−	−
CIMDL 9	P-ANCA	−/−	−	−	−	+
CIMDL 10	P-ANCA	−/−	−	−	+	+
CIMDL 11	P-ANCA	−/−	38.7	−	+	+
CIMDL 12	P-ANCA	−/−	−	0.504	+	−
CIMDL 13	P-ANCA	−/−	145	0.775	+	−
CIMDL 14	C-ANCA	−/−	112	0.836	+	−
CIMDL 15	C-ANCA	−/−	12.5	0.140	+	+
CIMDL 16	C-ANCA	−/−	139	0.405	+	+
CIMDL 17	C-ANCA	−/−	155	−	+	−
CIMDL 18	C-ANCA	−/−	>400	−	+	−
			WG			
WG 1	−/weak p-ANCA	−/−	−	−	−	−
WG 2	−/ND	−/ND	−	ND	ND	ND
WB 3	p-ANCA/−**	>1000/−**	−	−**	−**	−**
WG 4	p-ANCA/−**	84.7/−**	−	−**	−**	−**
WG 5	p-ANCA**	>1000/−**	−	−**	−**	−**
WG 6	p-ANCA**	203/−**	−	−**	−**	−**
WG 7	c-ANCA	−/−	115	−	+	−
WG 8	c-ANCA	−/−	+***	−	+	−
WG 9	c-ANCA	−/−	356	0.290	+	−
WG 10	c-ANCA	−/−	285.9	0.490	+	−
WG 11	c-ANCA	−/−	44.8	0.420	+	−
WG 12	c-ANCA/−**	−/−**	197.2	0.185**	−**	−**
WG 13	c-ANCA	−/−	10.1	0.417	+	−
WG 14	c-ANCA	−/−	257	0.210	+	−
WG 15	c-ANCA	−/−	132.5	0.340	+	−
WG 16	c-ANCA	−/−	>400	0.290	+	−
WG 17	c-ANCA	−/−	+***	0.660	+	−
WG 18	c-ANCA	−/−	30.6	0.350	+	−
WG 19	c-ANCA	−/−	108.5	0.300	+	−
WG 20	c-ANCA/ND	−/ND	69	ND	ND	ND
WG 21	c-ANCA§/ND	>1000††/ND	−	ND	ND	ND

Abbreviations: ND = not done.
*− = negative test result; + = positive.
†Negative: < 10 U.
‡Negative: < 15 U.
§Negative: < 0.099.
**A subsequent convalescent serum was evaluated at Mayo.
* **The assay used was an anti-acidic PMN granule extract assay.
††Different sera from this patient were tested repeatedly, always generating the same result.

Comparison of the imaging abnormalities detected in CIMDL and WG patients corroborated the clinical findings indicating that the severity of tissue destruction is much more severe in CIMDL than in WG patients.

Histopathologic findings

To determine which histopathologic features are discriminating for CIMDL and WG, we reviewed all nasal biopsy specimens of each patient. Of the 44 biopsy specimens obtained from the CIMDL patients, 19 showed nonspecific changes consisting of fibrosis with mild inflammation or extensive necrosis. The remaining 25 biopsies (57%) showed significant histologic abnormalities (Table 4). In all these biopsies, a dense inflammatory infiltrate of mononuclear cells admixed with neutrophils and eosinophils was present. Nuclear atypia was universally absent. The inflammatory cells frequently encroached upon the wall of venules and arterioles, resulting in variable degrees of narrowing of the lumen. The feature, referred to as

TABLE 3. Radiographic changes

Site involved	CIMDL	WG	Yates	$\aleph^2$
Septum	16	2	p<0.0000	p<0.0000
Inferior turbinates	12	0	p<0.0001	p<0.0000
Inferior turbinates (bilateral)	9	0	p<0.0017	p<0.0004
Middle turbinates	10	0	p<0.0006	p<0.0001
Middle turbinates (bilateral)	5	0	p<0.0515	p<0.0149
Superior turbinates	2	0	p<0.4652	p<0.1441
Lateral nasal wall	5	0	p<0.0515	p<0.0149
Lamina papyracea	1	0	p<1.000	p<0.3096
Hard palate	4	0	p<0.1088	p<0.0325
Soft palate	1	0	p<1.0000	p<0.3096

"perivenulitis," was found in 96% of the biopsies (Figure 4A). Microabscesses involving the wall of venules were found in 10 (40%) biopsies (Figure 4B). Obvious leukocytoclastic vasculitis with fibrinoid necrosis was identified in only 7 biopsies (28%) (Figure 4C). Other vascular changes detected in 7 (28%) biopsies consisted of fresh thrombi or sclerotic changes of the vascular wall, likely representing postthrombotic scars (Figure 4D). In 4 samples, the abnormalities involved medium-sized arterioles. It is noteworthy that the leukocytoclastic vasculitis and arteriolar thrombosis coexisted only in a single biopsy. Intra- or extravascular granulomas, scattered giant cells, or deep tissue necrosis with microabscesses were not found in any biopsy of the CIMDL patients.

When the histopathologic features of CIMDL patients with and without ANCA were compared, it appeared that occurrence of leukocytoclastic vasculitis was more frequent in the ANCA-positive than ANCA-negative patients (41.6% versus 20%, respectively). However, the difference did not reach statistical significance ($p = 0.6$).

The immunohistochemical composition of the mononuclear inflammatory cells showed a prevalence of CD3+ T cells, with a few CD56+ NK cells, and variable numbers of CD68+ macrophages. CD20+ B lymphocytes were rare or totally absent (data not shown). All biopsies were negative for infectious organisms as well as for birefringent foreign material. Immunohistochemical and in situ hybridization studies aimed at the detection of Epstein-Barr virus antigen and RNA were also negative (data not shown).

The histopathologic changes observed in biopsies obtained from the WG patients are also summarized in Table 4. Significant histologic abnormalities were noticed in 22 biopsies (76%). A dense inflammatory cell infiltrate, with cell composition, distribution, and immunohistochemical characteristics similar to those found in the CIMDL group was detected. Perivenulitis was recognizable in all biopsies (100%). Other vascular changes consisted of microabscesses in the vascular wall (50%), leukocytoclastic vasculitis with fibrinoid necrosis (64%), and fresh or organized thrombi (23%). Pathognomonic histopathologic features (15, 22) such as extravascular multinucleated giant cells (Figure 4E) or granulomas and microabscesses with deeply located necrosis (Figure 4F), were detected in 41% and 86% of biopsies, respectively.

In summary, biopsies with nonspecific changes were more frequent in CIMDL (44%) than in WG patients (24%), but the difference was not statistically significant. Microabscesses in the vascular wall and perivenulitis were observed with similar frequencies in both groups. Leukocytoclastic vasculitis and fibrinoid necrosis appeared to be more frequent in WG ($p = 0.02$). However, when the data analysis was based on the occurrence of the lesion in individual patients rather than individual biopsies, no difference was detectable: it occurred in 6 of 18 CIMDL and in 9 of 21 WG patients ($p = 0.11$). In contrast, extravascular changes consisting of stromal granulomas with giant cells, microabscesses, and deeply located necrosis were features exclusively encountered in WG ($p < 0.001$).

TABLE 4. Histopathologic features in nasal biopsies from 18 patients with CIMDL and 21 patients with WG

	CIMDL (no. biopsies/total)	WG (no. biopsies/total)	p Value (Fisher exact test)
Nonspecific changes	19/44	7/29	NS
Vascular changes			
Microabscesses in the vascular wall	10/25	11/22	NS
Lymphohistiocytic infiltrate ("perivenulitis")	24/25	22/22	NS
Thrombi (fresh or organized)	7*/25	5/22	NS
Granulomatous vasculitis	0/25	0/22	NS
Leucocytoclastic vasculitis and fibrinoid necrosis	7/25	14/22	0.02
Extravascular changes			
Single multinucleated giant cells or granulomas	0/25	9/22	<0.001
Microscopic foci of deeply located necrosis, associated or not with microabscesses	0/25	19/22	<0.001

*In 4 cases involving medium-sized arterioles.

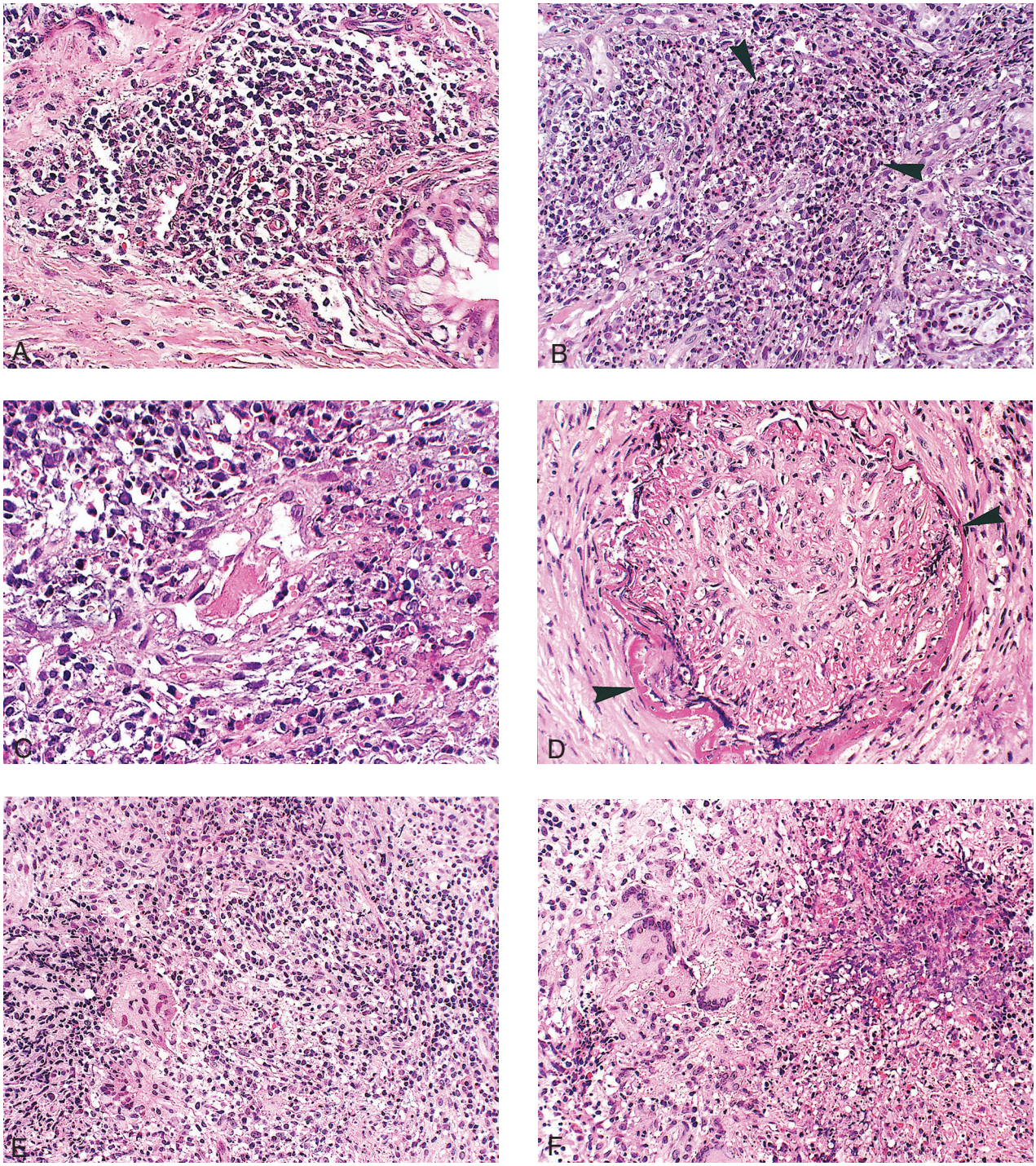

FIG. 4. Histopathologic features of nasal biopsies from cocaine-induced midline destructive lesions (panels A-D) and Wegener granulomatosis (WG) (panels E and F) patients. **A.** Dense polymorphic perivenular infiltrate, narrowing the lumen without obvious destruction of the vessel wall, referred to as "perivenulitis." **B.** The inflammatory infiltrate is particularly dense, and the formation of microabscesses within the vascular wall is recognizable (arrowheads). **C.** Fibrinoid necrosis and nuclear fragmentation identify leukocytoclastic vasculitis. **D.** The lumen of a small artery is occluded by scarlike tissue, probably resulting from an organized thrombus. Arrowheads indicate the external elastic lamina. **E** and **F.** Histopathologic features only seen in WG lesions are multinucleated giant cells scattered within a dense inflammatory infiltrate (**E**) and associated with deep tissue necrosis (**F**). All biopsies were stained with hematoxylin and eosin. (Original magnification for A, 190 ×; B, D, E, F, 95 ×; C, 285 ×).

Discussion

The abuse of cocaine may cause complications that can affect any organ system (16). Nasal septal perforation was first reported in 1912 (52). Despite the widespread abuse of cocaine, reports of CIMDL are scarce, and its incidence remains unclear. To our knowledge, only 24 cases with adequate clinical and pathologic documentation have been reported to date (4, 6, 8, 17, 20, 31, 38, 39, 43, 49, 58, 60, 62, 63, 66, 75). Only 5 of the reports (4, 17, 31, 62, 66) include ANCA test results, most of which were negative. The 2 reports of positive ANCA test results do not include target antigen specifications (4, 66). Based on its high specificity for the small vessel vasculitides including WG, a positive ANCA test result was thought to be of differential diagnostic value in this setting (62). In contrast, most of our patients presenting with CIMDL had ANCA. Because of this association they were at risk to be misdiagnosed as having WG. Indeed, some were initially treated with cytotoxic agents to no avail. Therefore, the identification of clinical, radiographic, and histopathologic features that allow a distinction between the 2 entities is important.

Clinical and radiographic differentiation of CIMDL and WG

Comparing the clinical and radiographic findings in patients with CIMDL with those of WG patients clearly indicates that the degree and localization of inflammatory changes differ substantially between the 2 groups. Furthermore, centrifugal progression of the necrosis from the nasal septum toward the nasal walls was apparent in CIMDL patients. In addition to the ubiquitous nasal septum perforation, most CIMDL patients had erosion of 1 (75%) or both (56.25%) inferior turbinates. Destruction of the middle turbinates (62.5%) occurred only in patients who also had inferior turbinate involvement. Among 18 cases reported in the literature with detailed imaging data (1, 2, 4, 8, 9, 17, 31, 38, 49, 60, 62, 66, 74, 75), 1 or both inferior turbinates were affected in all patients, and 1 or both middle turbinates were involved in 89%. The difference may reflect referral and reporting bias. Further destruction of the midfacial architecture involving the lateral nasal wall (medial maxillary sinus wall 31.25%, lamina papyracea 6.25%) or nasal floor structures (hard palate 25%, soft palate 6.25%) was always associated with involvement of inferior and middle turbinates. The notion of centrifugal progression is corroborated by the strong correlation between the extent of septal perforation and the number of nasal structures eroded. In contrast, erosion of structures of the midline was rare among WG patients (12.5%) and was limited to the nasal septum.

The localization of mucosal inflammation detected on imaging studies may provide further clues about the etiology. Hypointensity of mucosa and submucosal tissues on T2 and reduced or nonhomogeneous enhancement have recently been suggested as markers for granulomas and vasculitis in WG (47). In our study, these 2 abnormal MR signal patterns were not only detected in WG but also among cocaine abusers with similar frequency. In both patient groups, nonspecific inflammatory mucosal changes of the paranasal sinuses were identified. However, in CIMDL patients, signal intensity abnormalities were concentrated in the nasal septum and the turbinates. The central structures probably represent the areas of drug deposition. In contrast, the lesions had a more scattered distribution in WG, thereby reflecting more diffuse inflammation. Finally, abnormal enlargement and cystic changes of lymphatic tissue of the Waldeyer ring suggesting chronic reactive inflammatory changes were significantly more frequent in cocaine abusers.

Laboratory testing aimed at the detection of chronic or systemic inflammation, liver and kidney function abnormalities, infectious agents, and markers of autoimmunity revealed no significant abnormalities in CIMDL patients, representing a stark contrast between the severe destruction of the nose and an otherwise good health status.

It cannot be excluded that the observed clinical and radiographic differences between CIMDL and WG reflect referral bias. It is indeed possible that patients with cocaine-induced lesions seek medical attention only after substantial tissue damage has occurred. In contrast, WG patients may be identified earlier for several reasons including symptoms in other organ systems. However, when severe destruction of nasal structures, bony erosion, and signs of inflammation affecting the lymphoid tissue of the Waldeyer ring are encountered in the absence of systemic inflammatory changes, substance abuse should be suspected and carefully ruled out.

Histopathologic differentiation of CIMDL and WG

Histopathology remains the "gold standard" of diagnosis for WG, particularly in patients with disease limited to the upper respiratory tract. Biopsies of the nose and sinuses have a limited sensitivity which hinges on the identification of pathognomonic histopathologic features of WG in the specimen. Vascular changes including microabscesses in the wall of venules and leukocytoclastic vasculitis have been proposed as characteristic features of WG that should be sought in head and neck biopsy specimens (15, 19, 22). We found vascular changes including chronic perivenulitis, microabscesses, and frank leukocytoclastic vasculitis in the majority of CIMDL

patients (57%). In addition, thrombosis of venules and arterioles was found in the form of fibrin deposition or organizing intravascular granulation tissue. Consequently, the histologic changes observed in a large proportion of biopsies from patients with CIMDL might be misinterpreted as "consistent with WG" (15). Previous case studies of CIMDL reported mucosal biopsies showing nonspecific tissue necrosis and acute or chronic inflammation in the absence of vasculitis or granulomas (4, 31, 38, 49, 62, 66). This discrepancy is difficult to interpret because the timing and the size of the biopsies were not reported. It is possible that at our institution biopsies were performed early in the disease process and that the specimens were larger. The occurrence of vasculitis in nasal biopsies from cocaine abusers is not entirely unexpected, since cocaine-associated vasculitis has been reported to occur in other sites, such as the central nervous system and the skin (23, 25, 37, 44, 46, 51), and occlusive arteriolar lesions have been found in the gastrointestinal tract (33). Furthermore, in vitro experiments have documented increased adhesion of neutrophils and monocytes to endothelial cells, increased expression of endothelial adhesion molecules ICAM-1, VCAM-1, and ELAM-1, and increased expression of TNF-α and interleukin-6 (26), mechanisms that have also been implicated in ANCA-associated vasculitis.

Even though leukocytoclastic vasculitis appeared more frequently in nasal biopsies of WG than CIMDL patients, the finding does not exclude CIMDL. Furthermore, others have detected leukocytoclastic vasculitis in a much lower percentage of nasal biopsies from WG cases (22). Therefore, this histopathologic feature alone is of low sensitivity and specificity for WG.

Perivenulitis is characterized by a dense polymorphic infiltrate that surrounds the vessels and encroaches upon the vascular wall and narrows the lumen. It is not associated with leukocytoclasia or fibrinoid necrosis, but it can mimic genuine vasculitis. Similar vascular abnormalities have been reported in WG, with different interpretations ranging from chronic inflammation of the vessel walls to nonspecific changes (21, 22, 73). We found the feature in almost all biopsies from both groups and, therefore, believe it is nonspecific. Granulomatous vasculitis was not detected in any of the biopsy specimens of WG patients, in accord with the results of others (19, 22).

In contrast to the vascular changes, the nature of the extravascular inflammatory changes is more discriminating. Scattered multinucleated giant cells, granulomas, and extravascular foci of microscopic necrosis were identified in a large proportion of WG cases but not in any of the biopsies obtained from cocaine abusers. In conclusion, a definitive differential diagnosis between CIMDL and WG cannot be made on the basis of vascular changes on mucosal biopsies from the upper respiratory tract. However, it is possible, provided the specific extravascular changes of WG are found. This observation highlights the importance of extravascular changes in the histologic diagnosis of WG (14, 15, 24, 41). It also reemphasizes that WG is a necrotizing granulomatosis and a vasculitis, a view that was held by Wegener himself and others (15, 24, 41, 42, 64, 76).

ANCA in CIMDL

The high frequency of ANCA in patients with CIMDL was unexpected and raises questions about their etiology, their pathogenic significance, and whether they can be distinguished from the ANCA in WG. The positive ANCA tests in patients with CIMDL may lead to a clinical misdiagnosis, particularly if only IIF testing or antigen-specific ELISAs are performed in isolation. Several recent multicenter studies and consensus statements have called for the combined use of IIF and target antigen-specific testing, because only this combination maximizes the sensitivity and specificity of ANCA testing for vasculitis (30, 59). Indeed, very few well-documented occurrences of C-ANCA with matching PR3-reactivity and P-ANCA with matching MPO-reactivity have been reported in nonvasculitic conditions (10, 45, 53). Our data seem to confirm this only partially. None of the P-ANCA found in CIMDL patients reacted with MPO, whereas all P-ANCA found in the WG control population reacted as expected with MPO. Further testing revealed that 4 of the P-ANCA found in CIMDL patients reacted with PR3, a phenomenon which has been reported to occur occasionally, but not in patients with well-documented biopsy-proven WG (36, 69). Three of the P-ANCA - positive sera reacted with HLE, and 2 of them were positive for both PR3 and HLE, suggesting cross-reactivity or occurrence of different ANCA in the same specimen. Consequently, target antigen-specific analysis of the P-ANCA-positive sera reveals a clearcut difference from the P-ANCA seen in WG or microscopic polyangiitis.

The 5 C-ANCA-positive sera found in CIMDL patients represent more of a diagnostic challenge because they all reacted with PR3 in at least 2 target antigen-specific assays. More detailed testing revealed that 2 of them also reacted with HLE. The frequent occurrence of HLE-ANCA (5 of 13) may distinguish the ANCA of CIMDL from those of vasculitis. HLE-ANCA have been described in autoimmune diseases, but are extremely rare in vasculitis (12, 40, 48). Only 1 study using an ELISA for their detection reported 8 patients with HLE-ANCA among 108 WG patients and 15 among 78 microscopic polyangiitis patients (3). In the WG population presented here, no HLE-ANCA reactivity was found. Using the same HLE-ANCA detection

method applied here, we tested a cohort of 615 consecutive patients being evaluated for possible vasculitis and identified no HLE-ANCA in that patient population (56).

Finally, the fact that 2 of the 5 C-ANCA-positive sera (40%) were negative in the capture ELISA further sets these ANCA apart from those typically found in WG. These PR3-ANCA compete for the epitope on PR3 that is recognized by the capturing monoclonal antibody, MCPR3–2, an epitope that is recognized by less than 5% of PR3-ANCA from WG patients (57, 71).

The cause of ANCA in CIMDL patients remains unclear. In this context the observation that 4 of the 13 ANCA-positive CIMDL patients but none of the 19 ANCA-positive WG patients displayed double-reactivity is instructive. ANCA reacting with multiple target antigens at the same time have previously been noted in patients with drug-induced ANCA and vasculitis (reviewed in references 11, 34). Perhaps the ANCA response in CIMDL patients is the result of polyclonal B-cell stimulation by cocaine or drug adulterants similar to that induced by propylthiouracil, hydralazine, D-penicillamine, allopurinol, and others.

It is also possible that ANCA in CIMDL patients are related to infection with *S. aureus*, which was documented in most of the patients. This is consistent with reports linking the almost universal presence of nasal *S. aureus* in cocaine abusers to a high risk of infectious complications including toxic shock syndrome after nasal surgery (27). The mucosal damage caused by ischemia or by crystal-induced microtrauma may predispose cocaine users to the development of chronic low-grade infection with *S. aureus*. WG patients' nasal mucosa is also frequently chronically infected with *S. aureus*, and the carrier status has been linked to a higher relapse rate as well as to ANCA formation (70). Several mechanisms have been proposed to explain the role of *S. aureus* infection in ANCA formation (reviewed in reference 13). *S. aureus* releases toxins known to be powerful superantigens thought to activate T cells and B cells in an unrestricted manner, by circumventing the normal antigen-specific immune response. Furthermore, cell-wall components of *S. aureus* are known to be effective T-cell-independent B-cell mitogens that could induce autoreactive B cells to produce ANCA.

Many studies have reported ANCA in various infections (reviewed in references 10, 34). For most, the target antigens for the ANCA were not PR3 or MPO (10). However, C-ANCA reacting with PR3 have been well documented in subacute bacterial endocarditis (10) and in shunt nephritis (7). Streptococcal species were identified in 5 of the 7 reported endocarditis patients (10). Streptococcal species are also known to produce superantigens (18, 54). All patients recovered on antibiotic therapy, and ANCA disappeared after resolution of the infection (7, 10). In contrast, chronic infections of the necrotic CIMDL are almost impossible to eradicate. This may contribute to the persistence of ANCA in these patients.

PR3- and MPO-ANCA have been implicated in the pathogenesis of small vessel vasculitis (reviewed in references 32, 34, 50). At first, our finding of ANCA in CIMDL patients seems to speak against a pathogenic role of ANCA because none of the CIMDL patients developed any sign of vasculitis. Furthermore, the clinical presentation and histopathologic features did not differ significantly between CIMDL patients with ANCA and those without. However, there is growing evidence that different ANCA subsets may have different pathogenic potential. Many large studies performed during the last decade indicate that only ANCA reacting with the target antigens PR3 or MPO, and not those directed against other target antigens, are related to the development of vasculitis (reviewed in reference 34). In addition, PR3-ANCA and MPO-ANCA from vasculitis patients appear to recognize a restricted number of conformational epitopes (5, 67, 72). Some conformational PR3-ANCA epitopes, such as those displayed preferentially on the proform of PR3, seem to correlate more closely with vasculitis activity than others (55). Our more detailed characterization of the ANCA detected in CIMDL patients indicates both reactivity with target antigens other than those associated with vasculitis, and evidence that the PR3-ANCA found recognize a different spectrum of epitopes than the typical PR3-ANCA in WG.

Conclusion

We found a high frequency of positive ANCA test results in patients who presented for an evaluation of severe necrotizing nasal lesions associated with habitual nasal cocaine insufflation. As the drug use history provided by patients is notoriously unreliable, this finding may complicate the differentiation of cocaine-induced lesions from necrotizing granulomatous inflammation of the upper respiratory tract associated with WG. Careful physical, radiographic, and histopathologic examination of the CIMDL patients and all WG patients seen with nasal inflammation during the same time frame revealed significant differences between the groups. The localized destruction of nasal and facial structures is much more severe in CIMDL, whereas signs of systemic inflammation are universally absent. Vascular abnormalities mimicking vasculitis were frequently found in biopsy specimens of CIMDL patients and are not helpful in the differential diagnosis. However, extravascular necrosis, microabscesses, granulomas, and giant cells are differentiating histopathologic hallmarks of WG. Whereas routine ANCA testing does not clearly differentiate the ANCA found in some CIMDL patients from those of

WG patients, more detailed investigations suggest interesting differences between the ANCA of the 2 patient populations.

Summary

We compared the clinical, serologic, radiographic, and histopathologic features of 18 consecutive patients who presented with cocaine-induced midline destructive lesions (CIMDL) with those of all 21 patients with Wegener granulomatosis (WG) with nasal involvement evaluated during the same time period. Routine ANCA tests were positive in 13 of 18 CIMDL patients compared with 19 of 21 WG patients. Clinical and radiographic evaluation revealed that destruction of facial midline structures was significantly more severe in CIMDL than WG. In contrast to WG, there was no other organ involvement and no significant laboratory abnormalities indicating systemic inflammation in CIMDL. Histopathologic evaluation revealed the frequent occurrence of nonspecific inflammation, necrosis, and vascular abnormalities such as leukocytoclastic vasculitis and perivenulitis in CIMDL as well as in WG. Only extravascular microabscesses, necrotizing granulomas, and multinucleated giant cells found in WG were discriminatory features. More detailed analysis of the ANCA found in CIMDL and WG patients showed the following differences. Of 8 P-ANCA-positive CIMDL sera, none reacted with MPO, 4 reacted with PR3, 3 reacted with HLE, 2 of which showed double-reactivity with PR3 and HLE. All of 5 C-ANCA-positive CIMDL patients showed reactivity with PR3. Two of these also reacted with HLE. In contrast, all but 1 of the 19 ANCA-positive WG patients displayed concurrent P-/MPO-ANCA or C-/PR3-ANCA reactivity, respectively. In 1 WG patient the target antigen reactivity was reversed. None of the WG patients displayed double-reactivity. Consequently, routine ANCA testing does not allow an unequivocal distinction between CIMDL and nasal involvement of WG, but more detailed investigations suggest instructive differences between the ANCA immune responses of the 2 patient populations.

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