Sinonasal involvement in systemic vasculitides and cocaine-induced midline destructive lesions: Diagnostic controversies

M. Armengot, M.D., Ph.D., A. García-Lliberós, M.D., M. J. Gómez, M.D., A. Navarro, M.D., and A. Martorell, M.D., Ph.D.

ABSTRACT

Multiple systemic diseases produce various clinical manifestations in the sinonasal area. They usually appear as difficult-to-diagnose disease processes with slow, atypical clinical courses. The aim of this study was to evaluate the sinonasal manifestations of systemic vasculitides, highlighting key points for diagnosis and differential diagnosis with other pathological entities, especially cocaine-induced midline destructive lesions (CIMDL). A retrospective study was performed of 10 patients treated in our hospital during the last 5 years with an initial diagnosis of systemic vasculitides with sinonasal involvement: eight patients with granulomatosis with polyangiitis (GPA; new nomenclature for Wegener granulomatosis) and two patients with Churg-Strauss syndrome (CSS). The study variables were clinical presentation, nasal endoscopy results, maxillofacial scan results, nasal biopsy results, erythrocyte sedimentation rate, and autoimmune antibody levels. The definitive diagnosis was GPA in six (60%) patients, CSS in two (20%) patients, and CIMDL in two (20%) patients. Nasal symptoms were similar in all patients, but nasal polyps were present in only one patient with CSS. Systemic manifestations were absent in patients with CIMDL. Likewise, peripheral eosinophilia was observed only in the two patients with CSS. Specific positive biopsy specimens were obtained in six patients (all six patients with GPA, one with CSS, and one with CIMDL). Antineutrophil cytoplasmic antibodies (ANCA) were positive in all patients with GPA (proteinase 3 antigen in five patients and myeloperoxidase in one patient), and perinuclear ANCA was positive in one patient with CIMDL; however, this patient showed an undefined pattern. Finally, the response to treatment was adequate in all patients excluding those with CIMDL. GPA and CIMDL syndromes pose a difficult differential diagnosis because they have common clinical, serological, and histological presentations. Negative histological results do not exclude the diagnosis of sinonasal vasculitides. The absence of systemic manifestations and the lack of response to treatment will lead to the confirmation of CIMDL syndrome in a cocaine user. Otolaryngologists play an important role in the early and differential diagnosis of these diseases.

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Multiple systemic illnesses produce various clinical manifestations in the nose and paranasal sinuses. These manifestations may present as difficult-to-diagnose pathological processes with slow and atypical development. Lesions exhibiting a granulomatous or necrotizing aspect may be observed in certain systemic vasculitides; in inflammatory, chronic, autoimmune, neoplastic, traumatic, or infectious illnesses; and even in cases of substance abuse, primarily of cocaine, complicating the differential diagnosis list.[1] Cocaine-induced midline destructive lesions (CIMDLs) comprise a growing pathology and generate the greatest diagnostic difficulties because neither the histopathological results nor analysis provides conclusive information.

From the Department of Pathology, General and University Hospital, Ear, Nose, and Throat and Medical School, and Departments of Surgery and Pathology, Valencia University, Valencia, Spain

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Address correspondence and reprint requests to Miguel Armengot, M.D., Ph.D., Avda Mediterrani, 33, 46134, Foios, Valencia, Spain

E-mail address: miguel.armengot@uv.es

Sinonasal vasculitis illnesses affect small and medium arteries. The most common are granulomatosis with polyangiitis (GPA; new nomenclature of Wegener's granulomatosis[2]; up to 90% of cases) and Churg-Strauss syndrome (CSS; up to 69% of cases); the latter may be renamed eosinophilic GPA.[3] Microscopic polyarteritis (MPA) is found less frequently (in up to 30% of cases).[4]

The etiopathogenesis of these vasculitides is not well known, although the presence of antineutrophil cytoplasmic antibodies (ANCAs) is common, implicating a type II immunologic or cytotoxic mechanism. These antibodies present in different patterns. The perinuclear pattern (p-ANCA), which is directed against myeloperoxidase (MPO), and the cytoplasmic pattern (c-ANCA), which acts against proteinase 3 (PR-3), are characteristic of the previously mentioned types of vasculitis and provide important data for reaching a differential diagnosis. The p-ANCA is more common in CSS and MPA, and c-ANCA is more common in GPA. Regardless, low levels or atypical patterns of ANCA have been found in patients with CIMDL,[5] adding another element of diagnostic controversy to an already nonspecific clinical definition.

Diagnostic difficulty is increased by the fact that ANCA may take years to show a positive result, and the histopathological findings are often nonspecific,[6] only showing signs in cases involving acute and/or chronic inflammation.[7]

In this study, we retrospectively analyzed the sinonasal involvement in systemic vasculitides, highlighting key features for diagnosis and differential diagnosis in clinical, investigative, and histopathological findings. In this report, we also address the difficulty in reaching a differential diagnosis in patients with CIMDL.

MATERIALS AND METHODS

A descriptive retrospective study of 10 patients diagnosed with and treated for sinonasal vasculitis was performed during a 5-year period. Patients were referred to the Ear—Nose–Throat (ENT) Department when presenting with one or more of the following signs or symptoms: nasal obstruction, epistaxis, cacosmia, rhinorrhea, chronic atrophic rhinitis, saddle nose deformity, and expulsion of nasomucosal scabs.

Patient evaluation included the following: hemogram, serological and immunological tests (determined through immunofluorescence and antigen-specific MPO–ANCA and PR-3–ANCA), urinalysis, and chest x rays. ENT testing comprised nasal passage endoscopy with biopsies of suspicious sites and a maxillofacial scan.

Pathological diagnostic criteria were as follows: in GPA, the presence of two or more of the following morphological signs—vasculitis, necrosis, and intra- and extravascular granulomas; in CSS, necrotizing vasculitis, eosinophil infiltrates, and extravascular granulomas. There were no characteristic findings at this level in either MPA[8] or CIMDL.

For the histopathological evaluation, 11 mucosal biopsy specimens from the nasal cavities and paranasal sinuses were evaluated from all patients. One patient had more than one biopsy sample. The sections were stained with hematoxylin and eosin. Polarizing filters were used to identify birefringent foreign material.

After analyzing all described data, variables included in the study were age at diagnosis, sinonasal symptoms, other organs affected, findings from nasal exploration, maxillofacial scan results, nasal biopsy results, blood test results, toxic substance use, initial diagnosis, and definitive diagnosis.

RESULTS

The results are summarized in Tables 1 (clinical table) and 2 (exploratory and complementary test results).

Of the 10 patients, 8 were initially diagnosed with GPA and 2 were diagnosed with CSS disease. Two were cocaine users.

Table 1 **Nasal clinical signs and nasal examination findings**

	Sex/Age (yr)	Nasal Clinical				Nasal Examination			
		Rhinorrhea	Nasal Respiratory Insufficiency	Epistaxis	Olfactory Disturbance	Septal Perforation	Nasomucosal Scabs	Nasal Polyps	Ulceration
Case 1	F/42	Yes	No	Yes	Yes	Yes	Yes	No	No
Case 2	M/54	No	Yes	No	No	Yes	No	No	No
Case 3	M/37	Yes	No	Yes	No	No	No	No	Yes
Case 4	F/41	No	No	Yes	No	No	No	No	Yes
Case 5	M/63	Yes	No	Yes	No	No	Yes	No	No
Case 6	F/51	Yes	Yes	No	No	No	Yes	No	No
Case 7	F/52	Yes	Yes	No	No	No	No	Yes	No
Case 8	F/69	Yes	Yes	Yes	No	No	Yes	No	No
Case 9	M/44	No	Yes	No	No	Yes	Yes	No	No
Case 10	M/44	Yes	No	No	Yes	Yes, with orosinusal communication	No	No	No

F = female; M = male.

Table 2 **Extranasal clinical, complementary test and diagnosis**

	Extranasal Clinical	ANCA and Blood Eosinophilia	Histological Diagnosis	First Diagnosis	Final Diagnosis
Case 1	Polyarthralgia, cutaneus	c-ANCA PR-3	Nonspecific	WG	WG
Case 2	Polyarthralgia	c-ANCA PR-3	WG	WG	WG
Case 3	Polyarthralgia, cutaneus	c-ANCA PR-3	Nonspecific	WG	WG
Case 4	Pulmonary, renal and cutaneous	c-ANCA PR-3	WG	WG	WG
Case 5	Pulmonary, renal and neurological	c-ANCA PR-3	WG	WG	WG
Case 6	Polyarthralgia, pulmonary and renal	p-ANCA MPO	WG	WG	WG
Case 7	Pulmonary	Eosinophilia +/No ANCA	Nonspecific	CSS	CSS
Case 8	Pulmonary	Eosinophilia +/No ANCA	CSS	CSS	CSS
Case 9	No	p-ANCA without Ag	Nonspecific	WG	CIMDL
Case 10	No	Absent	Cocaine-related vasculitis	WG	CIMDL

WG = Wegener granulomatosis; CSS = Churg-Strauss syndrome; CIMDL = cocaine-induced midline destructive lesions syndrome; p-ANCA = perinuclear pattern antineutrophil cytoplasmic antibodies; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibodies; PR-3 = proteinase 3; MPO = myeloperoxidase.

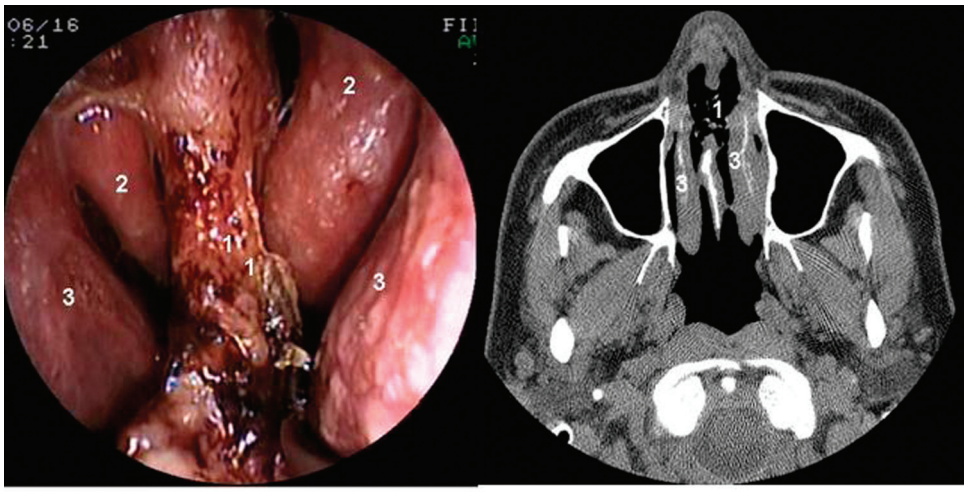

Figure 1. *(A) Endoscopic and (B) computed tomography (CT) view of granulomatosis with polyangiitis (GPA; patient 2, Tables 1 and 2). 1, septal perforation with scabby lesions in endoscopic view; 2, bilateral view of middle turbinates through septal perforation; 3, inferior turbinates; in endoscopic vision we can appreciate the granulomatous mucosal lesions.*

Nasal clinical signs are summarized in Table 1. Notably, patients with CSS mainly presented with epistaxis, rhinorrhea, and nasorespiratory insufficiency; further manifestations described pertained to patients with GPA and cocaine-related vasculitis.

The nasal examination findings are summarized in Table 1. Notably, nasal polyps were observed in only one patient with CSS. One patient presented with bone destruction in both maxillary sinuses and nostrils and a right sinonasal–oral fistula (Figs. 1 and 2).

Maxillofacial scans showed several degrees of mucosal and nasal thickening and reproduced the endoscopy findings (Figs. 1 and 2).

Systemic symptoms are summarized in Table 2.

Six biopsy specimens of the 10 patients had a definitive histological diagnosis: four were diagnosed with GPA (Fig. 3), one with CSS, and one with cocaine-related vasculitis (Fig. 4). Four biopsy specimens had no specific changes that allowed a pathological diagnosis. Eosinophilic infiltrates were observed in one patient with CSS. Necrosis and vasculitis were described in the other three biopsy specimens with nonspecific findings.

We observed peripheral eosinophilia in both patients with CSS. ANCAs were negative in those believed to have CSS before testing. Five of the eight patients initially suspected of having GPA had c-ANCA, with the specific antigen PR-3. One patient displayed the p-ANCA pattern with the specific antigen MPO, and

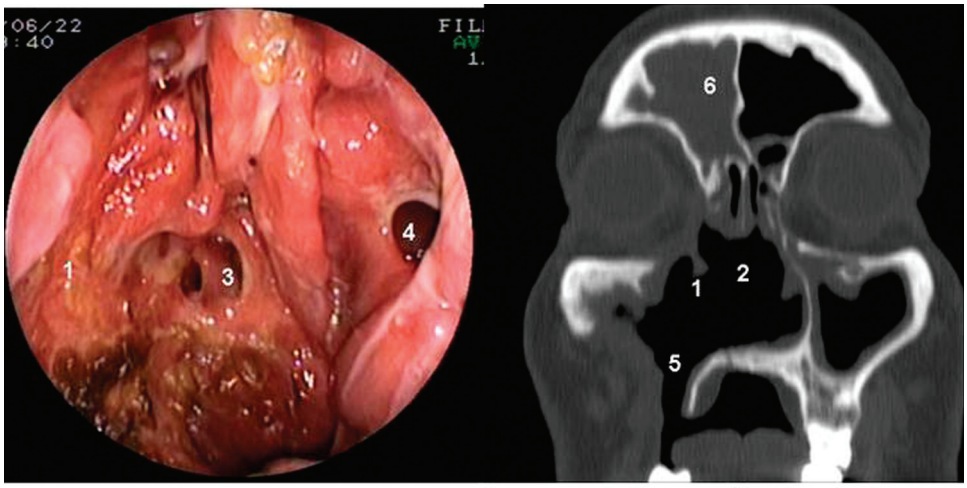

Figure 2. *(A) Endoscopic and (B) computed tomography (CT) view of cocaine-induced midline destructive lesion (CIMDL; patient 10, Tables 1 and 2). 1, Absence of right lateral nasal wall; 2, absence of nasal septum; 3, absence of anterior sinus sphenoidal wall; 4, left maxillary sinus with spontaneously widening of the ostium; 5, oronasal communication; 6, frontal sinusitis.*

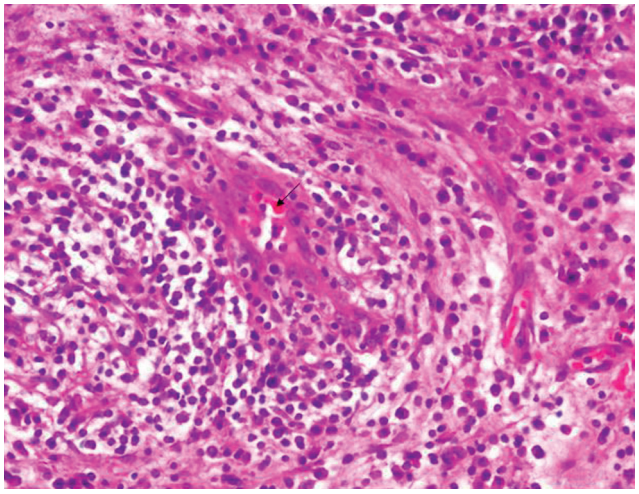

Figure 3. *Histopathology seen in a granulomatosis with polyangiitis patient, small-vessel vasculitis with infiltrating neutrophils in and around the vessels (arrow).*

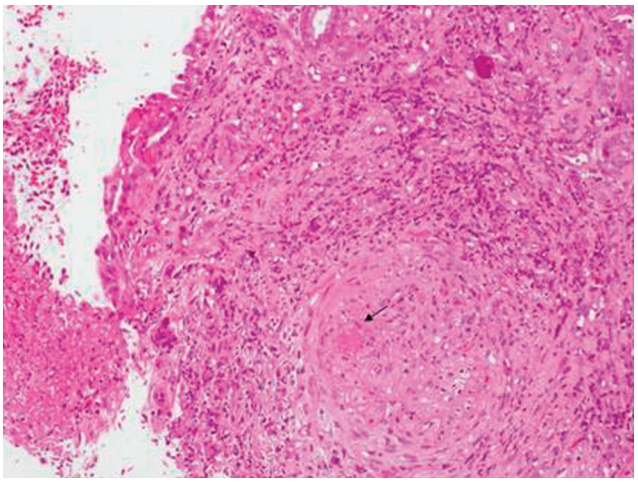

Figure 4. *Histopathological features of nasal biopsy specimens from cocaine-induced midline destructive lesions (CIMDLs). Ulceration of the epithelium with granulation tissue. Fibrinoid necrosis. The lumen of a small artery is occluded by scarlike tissue (arrow), probably resulting from an organized thrombus.*

one patient presented p-ANCA with an undetermined specific antigen (cocaine user).

Ultimately, the definitive diagnoses comprised six patients with GPA, two with CSS, and two with CIMDL. The initial diagnosis of GPA in the last two patients was discarded because apart from their cocaine use, they presented no accompanying systemic manifestations and did not respond to treatment with corticosteroids and cyclophosphamide. In one patient, the histopathological results were compatible with cocaine-related vasculitis.

DISCUSSION

A considerable number of patients with rheumatologic illnesses present with nasal signs and symptoms, which are helpful in establishing a definitive diagnosis. For this reason, evaluation of these patients should be multidisciplinary, including a detailed clinical history and exhaustive clinical examination and taking into account the multisystemic effects of these pathologies.

The results of our study indicate that the most frequently occurring systemic vasculitis with sinonasal manifestations is GPA, followed by CSS.

A key issue is differentiation of lesions stemming from autoimmune vasculitis and cocaine use, given that treatment and clinical results differ. The diagnosis can be reached by examining the clinical, analytical, and histopathological findings.

GPA is a systemic illness characterized by necrosis and granulomatous inflammation of the upper and lower airways in conjunction with small- and medium-vessel vasculitis, together with focal segmental or proliferative glomerulosclerosis.[7] It may manifest at any age, although it most frequently appears in individuals of ~40 years of age. Approximately 50–90% of patients

present with nasal signs and symptoms and nasal obstruction, rhinorrhea, and nasal scabs are most common,[9] as seen in our study. Given the frequency of these symptoms, which can appear in up to 19% of patients with rhinosinusitis, the formation of scabs, presence of septal perforations and ulcerations, and radiological findings help to reach a differential diagnosis.[10,11] Vasculitis is most frequently related to the presence of ANCAs (c-ANCA or p-ANCA), because they are present in 96% of all cases of severe granulomatosis and up to 83% of cases of limited granulomatosis.[1] These antibodies were observed in 100% of the cases in this study. The ANCA most often seen in GPA is c-ANCA–PR-3, which, according to some authors, and may be present in up to 95% of advanced-phase cases,[7] and appeared in 83% of the patients in our study. Other organs are frequently affected by GPA in the course of the illness, as observed in 100% of the patients in our study. In histological examinations, it is common for nonspecific chronic or acute inflammation to appear. In histological confirmation, three characteristic findings should be evident: necrosis, intra- or extravascular granulomas, and vasculitis. However, these findings are evident in only 15–25% of ENT biopsy specimens, and only one of the three criteria was evident in 65% of anatomopathologic specimens.[7] In our study, the pathological results met two of the criteria in 66% of the samples (four of six patients), and none of the results met all three diagnostic criteria. Ultimately, the diagnosis of GPA was based on the combination of clinical, histological, and serological findings.

CSS is a multisystemic medium- and small-vessel autoimmune vasculitis of unknown etiology. It can present at any age, although it most frequently affects middle-aged patients of both sexes fairly equally.[12] It is characterized by the onset of asthma in adulthood, hypereosinophilia, and extravascular eosinophilic granulomas.[12] The American College of Rheumatology[13] established six diagnostic criteria: a history of asthma, eosinophilia of >10%, mono- or polyneuropathy, migratory pulmonary infiltrates, paranasal pathology, and extravascular eosinophils in biopsy samples. The presence of four of the six criteria is sufficient for a diagnosis of CSS.[13] The most common manifestations of CSS are allergic rhinitis, recurrent rhinosinusitis, and sinonasal polyposis, thus affecting the ENT area. Some studies have observed the presence of sinonasal polyposis in up to 50% of cases, a figure that corresponds with the findings of our study.[14] Involvement of the paranasal sinuses and sinonasal polyposis are typically found in radiological studies, as also seen in our study. Fifty percent of patients with CSS have p-ANCA–MPO^+ antibodies,[1] although the presence of c-ANCAS–PR-3 also exists, a finding that we did not encounter given that none of the patients in our study were $ANCA^+$. When no positivity for this type of antibody is found, the diagnosis is not excluded if there is an elevated clinical suspicion. Although a histological study is not necessary for diagnosis, nasal biopsy specimens are taken to complete the examination. Compatible findings are necrotizing vasculitis, extravascular granulomas, and tissue eosinophilia. These findings are seldom encountered, and we found only one example of tissue eosinophilic infiltrates suggestive of CSS. Furthermore, this result is not found in biopsy specimens from nasal polyps.[1] Thus, as in the case of GPA, the specific combination of clinical, radiological, serological, and histological findings along with a high suspicion of the illness aids us in the final diagnosis.

We must also mention the importance of the differential diagnosis of the pathology produced by regular cocaine use (CIMDL). Evidence of this syndrome, characterized by destructive lesions in the nasal cavity and paranasal sinuses, can be seen on radiological images. The most frequent symptom is the appearance of self-limiting epistaxis, rhinorrhea, and scabs. These signs and symptoms may be difficult to distinguish from those normally observed in GPA, although in this syndrome, the lesions are fundamentally limited to the sinonasal area without affecting other ENT areas.[5] In terms of the presence of antibodies in these cases, ANCAs are also frequently detected, as they are in GPA. Unlike GPA, CIMDL manifests a characteristic p-ANCA pattern directed toward elastase or other nonspecific antigens.[15] However, this p-ANCA–elastase detection trial is not widely accessible in routine practice. From a histopathological perspective, CIMDL reveals extensive necrosis, and although acute inflammatory and chronic perivascular infiltrates are observed in some cases, the specific characteristics of GPA, such as granulomas, giant multinucleated cells, leukocytoclasia, or fibrinoid changes, are seldom seen.[5] The fundamental pillar for treatment is the cessation of cocaine use by the patient. To alleviate symptoms, nasal washes, antibiotics, and topical corticosteroids are used.[16] Some authors have observed that immunosuppressants such as cyclophosphamide or methotrexate are generally effective in vasculitis but ineffective in CIMDL.[5]

Levamisole, now available as a veterinary anthelmintic medication, has emerged as a prevalent adulterant of illicit cocaine use.[17] One case of $ANCA^+$ vasculitis from levamisole-tainted cocaine with concomitant CIMDL has been reported.[18] Six other cases of purpura, cutaneous necrosis, and positive p-ANCA after consuming levamisole-adulterated cocaine have been reported.[17]

Ultimately, the diagnosis in the two patients initially believed to have GPA in our study was made by taking the following characteristics into account: (a) The pres-

ence of sinonasal manifestations without systemic involvement; (b) the sole evidence of necrosis in the histological analysis and, in one case, indications of lesions produced by cocaine use; (c) the presence of p-ANCA directed to nonspecific antigens in one case; (d) cocaine use; and (e) unresponsiveness to treatment *via* immunosuppressants, unlike in GPA patients.

CONCLUSIONS

A definitive histopathological diagnosis of sinonasal lesions in patients with systemic vasculitides is difficult. In most cases, only partial criteria for a diagnosis are met (compatible and not characteristic data). As a result, a negative histopathological result in a nasal biopsy specimen should not eliminate vasculitis. However, typical findings of vasculitis in biopsy specimens can definitively confirm the presence of systemic vasculitis. Positive results for ANCAs may be found in GPA and CIMDL, although their absence should not eliminate these diagnoses. GPA and CIMDL both involve a complicated differential diagnosis given their common clinical, serological, histopathological, and imaging characteristics. The absence of systemic involvement and the unresponsiveness to treatment point to a diagnosis of CIMDL in a patient using cocaine. Final confirmation can be established after considering the findings of the present study and the combined clinical, analytical, and histopathological analysis of the case in question. A multidisciplinary approach is essential for the diagnosis and treatment of these illnesses. The otolaryngologist plays an important role in the early and differential diagnosis of these diseases.

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