Differential Diagnosis of Necrotizing Sinonasal Lesions

Kathleen T. Montone, MD

Context.—A number of entities may result in necrosis in the sinonasal tract and lead to significant morbidity and mortality. These include infections, necrotizing vasculitis, neoplastic processes, and drug dependency. This review will concentrate on the differential diagnosis of sinonasal necrotizing lesions.

Objective.—To review the differential diagnoses of necrotizing destructive lesions of the sinonasal tract.

Data Sources.—The current literature was reviewed to provide updated information regarding the differential diagnosis of sinonasal necrotizing lesions, including infectious disease processes; antineutrophilic cytoplasmic antibody–associated vasculitides; neoplastic processes, particularly natural killer/T-cell lymphomas; and drug abuse.

Conclusions.—The differential diagnosis of necrotizing sinonasal lesions is broad, with often overlapping diagnostic features that lead to diagnostic challenges. Ancillary tests such as special stains and immunohistochemical studies can offer significant assistance.

Invasive Fungal Rhinosinusitis.—Invasive sinonasal fungal infections frequently are considered in the differential diagnosis of lesions with sinonasal necrosis. Invasive fungal infections can be either acute (symptoms of <30 days duration) or chronic (symptoms present for >90 days).4–9 In the United States, the majority (>80%) of invasive sinonasal fungal cases are acute in nature.4

Acute invasive fungal rhinosinusitis (FRS) is most commonly seen in immunosuppressed patients, particularly those with hematologic malignancies and a low absolute neutrophil count.4–12 The fungal organisms invade tissue and blood vessels, resulting in tissue necrosis and infarction. Organisms can invade vital structures including the brain and large arteries. Acute invasive FRS is devastating and can be rapidly progressive, even fatal if not clinically and pathologically recognized. Grossly, the mucosa appears pale or necrotic because of vascular thrombosis from fungal invasion. The diagnosis of acute invasive FRS involves histopathologic identification of invasive fungi in tissue, which is often performed during intraoperative consultation (frozen section).10–12 Histologically, the mucosa shows infarction, vascular thrombosis, and little inflammation (Figure 1, A through C). Close review shows angioinvasion of fungal forms resulting in luminal thrombosis. Silver and periodic acid–Schiff stains are often useful in highlighting the organisms. Specific fungal agents can be identified by culture, immunohistochemistry, and in situ hybridization.13

The causative fungi are usually Aspergillus sp and Rhizopus sp; however, other fungal pathogens such as Fusarium sp and dematiaceous fungi may also be identified. Treatment with antifungal agents varies depending on the pathogen similar to many other necrotizing inflammatory processes of the sinonasal tract. A complete detailed presentation of sinonasal infections is beyond the scope of this review. This review will rather concentrate on some of the more commonly encountered necrotizing sinonasal infections.

Fungal Infections

Necrotizing Sinonasal Infections

The sinonasal tract is commonly involved by infectious agents including bacteria, viruses, fungi, and parasitic organisms.2,3 These infections can result in tissue necrosis and, chronically, can lead to midline destruction and deformity, similarly to many other necrotizing inflammatory processes of the sinonasal tract.
isolated. Drug resistance tests may guide treatment options and should be considered when fresh tissue is available.

Chronic invasive FRS is rare in the United States and is of 2 types: chronic invasive granulomatous FRS and chronic invasive FRS.5–7 These types of fungal infections are chronic in nature because of the length of time patients are symptomatic (>12 weeks by definition). Despite the fact that they are chronic in nature and slower to progress than acute invasive FRS, they do require aggressive therapy for adequate cure. Chronic granulomatous FRS is seen in immunocompetent patients, in contrast to the immunosuppressed patients in whom acute invasive FRS is seen, and is endemic to India, Sudan, and Africa.5–7 The infection is characterized by the presence of submucosal granulomatous inflammation, rare fungal hyphae, and extensive fibrosis.6,7 The most common cause is Aspergillus fumigatus.8

Chronic invasive FRS is a slowly progressive, low-grade invasive fungal infection that occurs most commonly in those with diabetes, those with acquired immunodeficiency syndrome, and steroid-treated diabetic patients and is most commonly associated with Aspergillus fumigatus.5–7 In contrast to granulomatous fungal sinusitis, fungal organisms are more numerous, there is a sparse inflammatory infiltrate, and occasionally there is angioinvasion.6,7 Both of these forms of fungal sinusitis should be treated by surgical debridement and systemic antifungal therapy.

**Rhinosporidiosis.**—Rhinosporidiosis is a chronic sinonasal fungal infection caused by Rhinosporidium seeberi, an organism infrequently encountered in the United States but endemic to India, Sri Lanka, South America, and Africa.5,6,8

There is higher prevalence in patients from those countries and they may be considered for this etiology/differential diagnosis. Grossly, the lesions present as a soft, friable hemorrhagic polyp. Histologically, the organisms are observed in the submucosa with a surrounding inflammatory cell infiltrate consisting of granulomatous inflammation with associated giant cells, neutrophils, lymphocytes, and plasma cells. Treatment involves surgery.

Several other fungal infections may also cause necrotizing, granulomatous sinonasal lesions including histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcosis. Most of them result from dissemination of pulmonary disease.2

**Bacterial and Mycobacterial Infections**

**Rhinoscleroma.**—Rhinoscleroma is a chronic upper respiratory tract infection caused by Klebsiella rhinoscleromatis, a gram-negative bacterium endemic to Central America, Egypt, Africa, India, and Indonesia and rarely seen in the United States.5,15,16 The infection is associated with overcrowding and poor hygiene. Biopsies reveal the characteristic finding of a submucosal lymphoplasmacytic infiltrate with large vacuolated histiocytes (Mikulicz cells) containing the bacterial organisms. If numerous, the bacteria can be seen on hematoxylin-eosin stain, but Gram, periodic acid–Schiff, silver, or immunohistochemical staining may be required to confirm the diagnosis. The end stage of the infection is characterized by significant fibrosis, which can result in respiratory failure. Although rhinoscleroma is clearly due to a bacterial infection, there have been reports of potential genetic predisposition with familial cases and the potential that the inflammatory reaction generated toward the organism may be related to a defect in immune regulation.5

**Syphilis.**—Another infectious cause of necrotizing nasal lesions is infection by Treponema pallidum, the etiologic agent of syphilis.2 Nasal disease secondary to T. pallidum can occur at any age, including in the neonatal period, and may be seen in primary, secondary, and tertiary syphilis. The necrotizing lesions can lead to bone and cartilage destruction with creation of a saddle nose deformity.

**Mycobacteria.**—Infection by Mycobacterium leprae causes leprosy, which is rare in the United States.5,17,18 The lepromatous form of the infection consistently shows nasal
involvement, with the septum and inferior turbinates most commonly involved. Like other chronic necrotizing infectious processes, septal perforation with saddle nose deformity and nasal atrophy can be seen. The histologic appearance of leprosy is characterized by the presence of large, foamy macrophages in the background of a chronic inflammatory cell infiltrate. Modified acid-fast stains (Fite) show acid-fast bacilli within these macrophages, and in addition, in situ hybridization can be used to speciate the organisms.19

*Mycobacterium tuberculosis* should also be kept in mind when evaluating a patient with a necrotizing nasal lesion.2 Tuberculosis of the nose usually arises secondarily from pulmonary disease, but it may occur as a primary lesion. Septal ulceration and septal perforation may be seen. The diagnosis is confirmed by staining for acid-fast bacilli and through culture, and biopsy may reveal the presence of necrotizing granulomas.

**Parasitic Infections**

*Leishmaniasis.*—Infection of the sinonasal mucosa by *Leishmania* sp can produce ulceration and necrosis, and longstanding infection produces erosion of the septum with facial deformity.2,3,20–23 Mucosal involvement alone is very rare, but when present almost always involves the sinonasal mucosa. Diagnosis is usually made by identification of the organisms in tissue or cytologic specimens with material taken from the ulcer base. Histologically the 1.5- to 3-μm organisms are present within histiocytes and can be identified on hematoxylin-eosin and Giemsa stains on smears.2,20–23 In tissue sections, Giemsa stain is not usually helpful, but the organisms may be highlighted with Brown and Hopps modified Gram stain and more specifically using immunohistochemistry and in situ hybridization.2,20–24 Differential diagnosis includes small fungi like *Histoplasma capsulatum* and *Penicillium* sp. The complications of mucosal infection include secondary bacterial infections, bleeding, and disfigurement. Mortality is usually related to secondary bacterial infections.

**Autoimmune Disease/Vasculitis:**

**Antineutrophilic Cytoplasmic Antibody–Associated Vasculitides in the Sinonasal Tract**

Necrotizing vasculitides associated with antineutrophil cytoplasmic antibodies (ANCAs) include granulomatous polyangiitis (GPA), formerly known as Wegener granulomatosis, and Churg-Strauss syndrome. Both of these entities may involve the sinonasal tract, although GPA more commonly does.2,3,25–28 Granulomatous polyangiitis is a necrotizing vasculitic process associated with cytoplasmic antinuclear cytoplasmic antibodies (c-ANCA). It is a systemic disease that is most commonly associated with necrotizing granulomatous vasculitis of the upper and lower respiratory tract and kidneys. Patients with GPA have autoantibodies to proteinase 3, a protein found in neutrophilic granules, although not all GPA is related to ANCs. Although GPA is of unknown etiology, the pathogenesis is believed to be multifactorial, with a combination of environmental, toxic, genetic, and likely infectious factors involved.2,3,25–28 Although infection is believed to be important in disease pathogenesis, a specific organism has not been identified in humans. More than 85% of patients present with sinonasal involvement, with the nasal septum being most commonly involved. Untreated disease can lead to cartilage destruction with saddle nose deformity and eventually patient death. Histologically, necrotizing vascu-

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**Figure 1.** A, Low-power view of a sinonasal biopsy showing vascular thrombosis and hemorrhage with minimal inflammation characteristic seen in patients with acute invasive fungal rhinosinusitis. B, High-power view of sinonasal mucosa showing tissue necrosis and fungal forms invading tissue. Cultures grew Rhizopus species. C, High-power view of invasive fungal organisms adjacent to sinonasal bone. Cultures grew Rhizopus species (hematoxylin-eosin, original magnifications ×25 [A], ×100 [B], and ×200 [C]).
litis and inflammation consisting of histiocytes, lymphocytes, plasma cells, and multinucleated giant cells surrounding geographic areas of basophilic necrosis are characteristic2,25–28 (Figure 2, A through D). A diagnosis of GPA is difficult to make on nasal biopsies and usually multiple biopsies are necessary before a definitive diagnosis can be rendered.

Churg-Strauss syndrome is a rare ANCA-associated vasculitis (usually perinuclear ANCA) syndrome characterized by bronchial asthma, systemic necrotizing vasculitis, and peripheral eosinophilia. Although uncommon, the disease may present with sinonasal involvement.3,29 Sinonasal tract involvement consists of sinonasal polyps and chronic sinusitis with eosinophils. Necrotizing vasculitis is only rarely seen in sinonasal specimens.

MALIGNANT NEOPLASMS

A variety of malignant neoplasms can cause ulcerative lesions of the nasal cavity, including carcinoma and lymphomas. The most common lesion to present as a necrotic midline destructive lesion is extranodal natural killer (NK)/T-cell lymphoma, nasal type.

Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type (angiocentric lymphoma/CD56 lymphoma), is a group of high-grade, Epstein-Barr virus–associated aggressive lymphomas that have a propensity to occur in the nose and paranasal sinuses, although these lymphomas may be seen in the skin, liver, and gastrointestinal tract.30–34 Other names for this lymphoid neoplasm include lethal midline granuloma, polymorphic reticulosis, and midline malignant reticulosis, although the preferred terminology currently is extranodal NK/T-cell lymphoma, nasal type. These tumors are more commonly seen in males and most commonly seen in Asia as well as Central and South America.30–34 The diagnosis is often difficult to make and is especially challenging early in the disease because patients initially present with nonspecific symptoms including nasal discharge, sinusitis, and headaches. Over time, the lesion becomes more destructive with extensive mucosal ulceration and destruction of bone and cartilage. Histologically, early lesions may be difficult to diagnose because the polymorphic lymphoid population lacks cytologic atypia. More advanced lesions are character-
Figure 3. A, Low-power view of a natural killer (NK)/T-cell lymphoma showing extensive necrosis. B, Low-power view of extensively necrotic sinonasal mucosa. This biopsy showed no viable cellularity. Extensive necrosis should alert the pathologist to the possibility of NK/T-cell lymphoma. Additional biopsies confirmed the presence of lymphoma in this patient. C, Extensive necrosis surrounded an atypical lymphocytic infiltrate in a patient with NK/T-cell lymphoma. D, Small artery infiltrated by atypical lymphocytic infiltrate in a patient with malignant lymphoma. E, Epstein-Barr virus–encoded RNA expression in perivascular atypical lymphoid cells. F, Medium power of sinonasal biopsy originally called benign showing a dense, bland lymphocytic infiltrate without necrosis. On subsequent biopsy, a diagnosis of NK/T-cell lymphoma was made (hematoxylin-eosin, original magnifications ×25 [A and B], ×100 [C and F], and ×50 [D]; diaminobenzidine and hematoxylin counterstain, original magnification ×50 [E]).
ized by the presence of large atypical lymphocytes admixed with smaller lymphocytes, plasma cells, and histiocytes (Figure 3, A through F). The tumor cells often infiltrate large blood vessels, resulting in tissue necrosis and infarction, and histologically can resemble GPA. The presence of extensive coagulative necrosis can make diagnosis difficult to make in small biopsies. The lesional cells are positive for CD56, a marker for NK cell differentiation; CD2; CD3e; CD7; and CD8, and are often negative for CD3, CD5, CD16, and CD57. The NK/T-cell lymphomas often express TIA-1, granzyme, perforin, and FAS. Epstein-Barr virus is almost always identified in lesional cells. Both p53 and c-kit mutations have been described; interestingly, p53 mutations are more commonly seen in Japanese patients and c-kit mutations in Chinese patients, indicating a diversity of tumors in different geographic locations. The prognosis for disseminated disease is poor.

**Epithelial Neoplasms**

Although all epithelial neoplasms may be associated with the presence of extensive sinonasal necrosis, a more recently described entity that deserves to be mentioned in the differential diagnosis of necrotic sinonasal lesions is that of NUT midline carcinoma, a tumor characterized by translocations of the nuclear protein in testis (NUT) gene on chromosome 15. Histologically, these lesions are highly aggressive, are undifferentiated, and often, but not always, show areas of abrupt squamous differentiation. Immuno- histochemistry to detect the NUT protein has proven to be useful for diagnosing this underrecognized entity.

**COCAINE-INDUCED MIDLINE DESTRUCTIVE LESIONS**

Cocaine abuse has been associated with the development of cocaine-induced midline destructive lesions (CIMDL) in the sinonasal area. Short-term cocaine use can lead to mucosal ulceration and necrosis. Long-term use has been associated with ischemia of not only the mucosal tissue but cartilage and bone, resulting in midline deformity and septal/palatal perforations. Histologically, one can see significant granulomatous inflammation, infarction, necrosis, and giant cell reaction (Figure 4, A through C). Necrotizing vasculitis may be evident. As a result, CIMDL shows clinical and histopathologic overlap with other midline destructive lesions, particularly GPA. Interestingly, CIMDL can be associated with the presence of ANCA, making distinction from overlapping vasculitic syndromes difficult. The etiology of CIMDL is not clear. It is believed that ANCA development may be related to bacterial superinfection of mucosal ulcers. In addition, CIMDL may actually be autoimmune in origin, which likely explains why CIMDL is a rare entity compared with the number of individuals believed to abuse cocaine. The ANCA in CIMDL is often perinuclear ANCA and targets human neutrophil elastase, but patients can also have c-ANCA targeting P3, and therefore the distinction from GPA can be difficult. The pathogenesis of cocaine in the development of CIMDL likely involves vasoconstriction resulting in ischemia and resulting mucosal and bone/cartilage necrosis, but recent evidence also implicates the possibility of levamisole (which is a known contaminant in cocaine) playing a role in CIMDL. It is believed that levamisole induces the autoimmune reaction because this agent has been associated with necrotizing vasculitis in other areas of the body. Most importantly, although CIMDL may be associated with the presence of ANCA, CIMDL does not respond to immunosuppressive therapy like GPA. It is highly recommended that one perform urine or serum drug testing in patients with midline destructive disease either at initial presentation or if a patient fails initial treatment.
IDIOPATHIC MIDLNE Destructive Disease

Despite extensive workup, in some cases the etiology of midline destructive disease remains unknown. However, recent investigators have identified additional entities associated with development of midline sinonasal destruction. Della-Torre et al described 4 patients who presented with 2- to 3-year histories of midline destructive diseases including saddle nose deformity who had extensive workup for infection, vasculitis, and neoplasia, particularly NK/T-cell lymphoma. Histopathologic review showed characteristic findings of immunoglobulin (Ig) G4-related disease including storiform fibrosis, lymphoplasmacytic inflammation, and >40% IgG4-positive plasma cells. Similarly, De Ravin et al observed a young male patient with hypomorphic mutations in recombination activating gene 1 (RAG1) who developed granulomatous midline destructive disease following thymectomy for myasthenia gravis. These newly described associations may explain some idiopathic causes of midline destructive disease.

In conclusion, the differential diagnosis of necrotizing intranasal lesions is extensive. Workup includes obtaining an extensive clinical history including recreational drug use history, histopathologic examination, and appropriate microbiologic and serologic workup to determine if infection or autoimmune or neoplastic disease processes are causing the midline symptoms. Despite extensive workup, there will be cases in which the etiology of the necrotizing process will remain indeterminate.

References