Chapter 40: Manifestations of Systemic Disease

Thomas J. McDonald

Despite advances in histopathologic and histochemical methods and our increasing knowledge of autoimmune disorders and diseases produced by infectious agents, systemic diseases manifesting themselves in the nose, paranasal sinuses, and nasopharynx continue to be overlooked sometimes by the otolaryngologist - head and neck surgeon. Definitive diagnosis is often delayed, sometimes with poor outcomes.

One of the reasons for this delay is that these diseases remain capricious and insidious. The early stages of Wegener's granulomatosis (WG) involving the nose, mimic an early respiratory tract infection. The earliest manifestation of so-called polymorphic reticulosis (PMR) (a T-cell lymphoma) often mimics acute unilateral sinusitis with orbital cellulitis and is treated as such in error. Intranasal sarcoidosis often presents with nasal obstruction, suggesting vasomotor rhinopathy.

The problem is that with the influx of refugees into the USA, the increasing tendency for people to travel outside of the USA, and the significant escalation in the number of the patients with all forms of acquired immunodeficiency syndrome (AIDS), the prevalence of systemic diseases of the nose and paranasal sinuses, especially tuberculosis, is increasing (McDonald, 1989; Sooy, 1987).

This chapter describes 15 systemic diseases with nasal and paranasal manifestations. These systemic diseases with nasal manifestations are categorized as follows: (1) autoimmune and connective tissue, (2) lymphoma-like, (3) granulomatous, and (4) infectious.

The selection of these categories is not easy and overlap occurs. For example, WG is one of the vasculitides as well as being considered granulomatous. It is also an autoimmune disorder. PMR continues to be called lymphomatoid granulomatosis, although there really is no granulomatous component present. Although sarcoidosis is categorized separately from tuberculosis in this chapter, recent interesting studies are shedding new light on the relationship between these two diseases.

Autoimmune and Connective Tissue Disorders

In 1897, McBride (1897) reported a case of rapid destruction of the nose and face. Since then, terms such as *lethal midline granuloma, malignant granuloma, malignant midline reticulosis,* and *Stewart's granuloma* have been popular. Many of these lesions were: (1) true neoplastic processes such as squamous cell carcinoma, (2) destructive lesions caused by tuberculosis and fungal infections, (3) diseases secondary to metabolic states as in diabetes gangrenescens, (4) true malignant lymphoma, and (5) processes secondary to vasculitis. Now, with precise histopathologic examination and better discourse between surgeon, pathologist, and general internal medicine colleagues and, more recently, with the use of genetic probes, abnormal

clonal genetic sequences in the DNA can be identified and more precise terminology can be used. In addition, even more recently, the anticytoplasmic autoantibodies (ACPA) test has been introduced (Gaughan et al, 1990; Specks and DeRemee, 1990; Specks et al, 1989).

Therefore, after specific causes are excluded, I prefer to use three clear terms to describe destructive lesions of the nose and face, with or without involvement of the paranasal sinuses, that often present with systemic findings. These are *WG, PMR (T-cell lymphoma),* and the rare *idiopathic midline destructive disease (IMDD).*

Wegener's granulomatosis

WG is systemic vasculitis with preferential involvement of the respiratory tract. It was named after Friedrich Wegener (1939) who first recognized the syndrome as a distinct disease entity. Until the first report of limited forms of WG by Carrington and Liebow (1966), the disease was viewed as one that could only be diagnosed if it presented as a classic triad (upper airway, pulmonary, and renal involvement). We now know that this is not the case and understand that limited forms can occur. The "ELK" classification proposed by DeRemee et al (1976) has proved to be useful for clinical practice. Patients are classified according to the extent of organ system involvement observed during the course of the disease. "E" stands for ear, nose, and throat involvement; "L", for lung involvement; and "K", for kidney involvement. The disease is considered to be represented by a continuum, usually beginning with limited organ involvement, which can be controlled, or progressing with unpredictable speed into the classic generalized form: a disseminated vasculitis with upper airway, lung, and kidney involvement.

From the otolaryngologist - head and neck surgeon's point of view, major advances have been made in the diagnosis and treatment of WG. These include better dialogue between internal medicine colleagues, pathologists, and otolaryngologists. Another major advance has been the development of the ACPA test for the diagnosis and follow-up of WG. For the repair of nasal dorsal defects, we now prefer cranium to rib cartilage.

Clinical features: limited forms

Patients usually present with airway symptoms such as nasal obstruction, blood rhinorrhea with crusting, vague pain over the nose, and nasal dorsum tenderness. It is not surprising that the initial manifestations are often confused with those of an upper respiratory tract infection that is prolonged. The findings in these patients include diffuse mucosal ulceration of the nose with ulceration of the posterior surfaces of the vomer, with or without nasal septal perforation. Although it is rare, we have also seen patients with strictly unilateral nasal involvement. There may be associated otologic, orbital, or upper tracheal involvement.

Diagnosis: laboratory investigations

All patients suspected of having WG should have a complete blood cell count, chemistry group (measurement of serum creatinine level is critical to evaluate renal function), urinalysis,

erythrocyte sedimentation rate, ACPA test, chest radiograph, and rheumatoid factor. In many, if the disorder is detected early and nasal biopsy is positive, the ACPA test will be positive, but many of the other tests may be within normal limits. For example, there may be a mild anemia, minimal elevation of the erythrocyte sedimentation rate (eg, 30-50 mm in 1 h), normal serum creatinine, urinalysis, and negative chest radiograph. General examination by colleagues in rheumatology or thoracic medicine may be normal and this form of "limited WG" can be treated with trimethoprim-sulfamethoxazole, one double-strength tablet twice daily. The mechanism of action of trimethoprim-sulfamethoxazole in the treatment of WG is unknown at this time. Perhaps a specific susceptible infectious agent is an underlying cause of WG. Regardless of the action, the use of this drug in these patients has precluded the use of immunosuppressive agents. Further study will be necessary to define its action.

More severe forms

Because we feel WG is represented by a continuum, other sites may be involved by the time the diagnosis is made or the process may have a rapid course. Lung involvement is typified by multiple cavitating lesions. There may be cutaneous involvement (tick-bite lesions on the lower extremities), and renal involvement (usually a nonspecific glomerulonephritis) is associated with an abnormal urinary sediment and elevated serum creatinine levels. When all three sites are involved (ELK), the systemic features are those of severe malaise, weakness, night sweats, and arthralgias.

Accordingly, the other laboratory tests will be significantly abnormal - highly elevated erythrocyte sedimentation rate (above 100 mm in 1 hr), marked anemia, and an ACPA test with a very high titer.

The nasal biopsy

The most important factor in the diagnosis is the nasal biopsy. A nasal biopsy specimen is taken, preferably in the operating room under topical cocaine anesthesia supplemented by intravenous sedation. The nasal crusts must be removed and a biopsy specimen of the typical underlying nasal mucosa is taken. Many representative tissues must be obtained in order to allow the pathologist to document the classic histopathologic findings. As with fungal diseases, tissue must be sent for specific acid-fast and fungal cultures to rule out fungal or tuberculous infections that have clinical and histopathologic findings similar to those of WG.

Treatment

In addition to the use of trimethoprim-sulfamethoxazole for limited forms, moderately ill patients with more than one site involved can be treated with either corticosteroids (60 mg/day) or cyclophosphamide (Cytoxan) (2 mg/kg/day). Patients who exhibit a fulminant course, however, should be treated with higher doses of corticosteroids (eg, 80-100 mg/day). As the disease responds (eg, serum creatinine levels improve), cyclophosphamide can be introduced while the corticosteroid dosage is lowered slowly.

The anticytoplasmatic autoantibodies test in Wegener's granulomatosis

WG has been considered an autoimmune disease. The anticytoplasmic autoantibodies test is based on the presence of serum antibodies directed against cytoplasmic components of neutrophils in patients with this disease. These IgG antibodies, present in the serum of patients with WG, cause a characteristic diffuse cytoplasmic granular staining pattern in cytospin preparations of neutrophils isolated from the blood of normal donors. The antibodies that cause this characteristic pattern were originally termed *anticytoplasmic autoantibodies* (ACPA); others now use the term *antineutrophil cytoplasmic antibodies* (ANCA) synonymously.

In order to avoid confusion, a new terminology was accepted by the participants at the recent Second International Workshop on ANCA held in the Netherlands in May 1989. The terms *c-ANCA* for cytoplasmic staining of antineutrophil cytoplasmic antibodies and *p-ANCA* for perinuclear (nuclear) staining of antineutrophil cytoplasmic antibodies will be used until all the antigens are identified unequivocally. An extremely high specificity of c-ANCA for WG, in excess of 90%, has been documented repeatedly in several large series. No positive c-ANCA results have been detected in patients with various forms of collagen vascular disease, including relapsing polychondritis (RP).

Histopathologic features

A frequent finding is inflammation of the mucosa and submucosa, with extensive necrosis and ulceration. Predominantly epithelioid necrotizing granulomas and vasculitis involving small arteries and veins are also evident. Some granulomas are nonnecrotizing, other have fibrinoid necrotic zones, and still others contain a central microabscess. Vasculitis can be identified as a variable degree of transmural infiltration of the vessel walls, often overshadowed by the inflammatory reaction of the necrotizing granuloma. Fibrinoid necrosis can be identified. Focal vascular lesions, healing vasculitis with vascular and intramural fibrosis, and focal loss of elastic tissue are also seen. In addition, granulation tissue containing cells of chronic inflammation, occasionally with abundant eosinophils, is evident.

Adjunctive treatment

In addition to the immunosuppressive treatment already described, I suggest daily nasal irrigation with either water or saline, followed by the application of aromatic lubricating agents such as oil of sesame with rose of geranium.

Lupus erythematosus

The type of lupus erythematosus (LE) that involves the nose is called *discoid LE* (DLE), and patients who have this disorder in a localized form have discoid lesions localized above the neck (Arnold et al, 1990). It is far more common than the generalized form. Nasal involvement is characterized by dull, red macules with adherent scales extending into patulous follicles, telangiectases, and atrophy. The patches tend to heal centrally first with atrophy, scarring,

dispigmentation, and telangiectasia.

Treatment

Flatter, scaly lesions can be treated with topical corticosteroids. More diffuse lesions across the bridge of the nose can be treated with triamcinolone (2.5 mg/mL in suspension) infiltrated into the lesion through a 30-gauge needle at intervals of 4 to 6 weeks. LE causing intranasal manifestations is uncommon. When it does occur, there is dryness with nasal septal ulcers and often perforation of the anterior nasal septum. The pathogenesis of nasal septal perforation is most likely small vessel disease with local ischemia and infarct. Treatment is the same as for any other nasal perforation, namely, good nasal care with nasal irrigation, the application of aromatic oils (oil of sesame and rose of geranium), and the fitting of a Silastic button, performed as an office procedure under topical anesthesia, if needed. This is a better alternative than local flap reconstruction.

Relapsing polychondritis

Relapsing polychondritis (RP) is a connective tissue disorder and also an autoimmune disease. It is characterized by intermittent episodes of inflammation of articular and nonarticular cartilage leading to chondrolysis, dystrophy, and atrophy of the involved cartilage (McCaffrey et al, 1978). Diagnosis is based on clinical criteria and is made by noting the typical redness, pain, and swelling of two or more cartilaginous sites at any one time. Typically, the cartilages of the pinna, nose, trachea, larynx, ribs, joints, and eustachian tubes are involved.

The nasal manifestations of this disease are typified by inflammation of the cartilage of the nasal dorsum, with eventual collapse and saddle-nose deformity. The intranasal and nasopharyngeal mucosa are usually spared, although there can be mild nasal dryness; this distinguishes the nasal involvement of RP from that of WG. Other head and neck involvement includes conductive hearing loss, sensorineural hearing loss, and vestibular disturbances. Ocular disease most often presents as conjunctivitis, nonspecific episcleritis, or iritis.

Autoimmune mechanisms appear to be responsible for this disease. Cell-mediated immunity to cartilage has been demonstrated in vitro, with the degree of response correlated with disease activity.

Treatment consists of either antiinflammatory agents (salicylates), intermittent use of corticosteroids, or dapsone. The principles underlying the safe use of dapsone are covered in another chapter, *The External Ear: Manifestations of Systemic Disease.*

Sjögren's syndrome

In 1933, Sjögren (Doig et al, 1971) described a triad of (1) keratoconjunctivitis sicca, (2) xerostomia, and (3) rheumatoid arthritis. The rheumatoid arthritis may be replaced by scleroderma, mixed connective tissue disease, polyarteritis nodosa, polymyositis, or systemic LE.

From the point of view of the otolaryngologist, xerostomia is an extremely prominent sign as is dryness of the eyes. Involvement of the nose consists of dryness of the nasal mucous membranes, leading to nasal crusting and hyposmia. Septal perforations are rare but do occur. A lower-lip biopsy is more useful than a biopsy of the septal mucosa. Under local anesthesia in the office setting, several small pieces of tissue containing mucosa and submucosal tissue should be taken from inside the lower lip. In Sjögren's syndrome, the classic findings are a dense lymphocyte infiltrate with many plasma cells involving the minor salivary gland cells.

Laboratory findings include a positive test for rheumatoid factor, an increased level of serum globulin and C-reactive proteins, and high titers of IgG, IgA, and IgM. Cryoglobulins may also be demonstrated.

Treatment for Sjögren's syndrome is directed at the artificial lubricants for oral and nasal dryness and artificial tears for eye symptoms.

Patients with Sjögren's syndrome are predisposed to the development of lymphoreticular malignancies such as non-Hodgkin's lymphoma. A rapidly increasing, firm enlargement of the parotid gland is particularly suggestive of evolution to malignant lymphoma.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is characterized by necrotizing vasculitis affecting small- and medium-sized vessels in the subcutaneous tissue and sometimes adjacent veins (Arnold et al, 1990). No single clinical picture is seen. Systemically, any vessel can be involved throughout the entire body. The major protean manifestations include hypertension, tachycardia, fever, edema, and weight loss. Mononeuritis multiplex with footdrop is a hallmark of PAN. Nasal involvement in PAN is usually reflected in nonspecific nasal mucosal lesions.

Behcet's disease

Behcet's syndrome is also called *oculo-oral-genital syndrome* and consists of recurrent oral aphthous ulcerations associated with any two of the following: uveitis, cutaneous vasculitis, synovitis, meningoencephalitis, or genital ulcerations (O'Duffy et al, 1984).

The nose is not as commonly affected as are the lips, tongue, buccal mucosa, soft and hard palates, tonsils, and pharynx. When lesions do occur, they can be single or multiple, 2 to 10 mm in diameter or larger, and sharply circumscribed with a dirty grayish base and a surrounding bright red halo.

Other head and neck involvement includes ocular lesions associated with intense periorbital pain and photophobia and retinal vasculitis, which is the classic eye sign and the chief cause of blindness associated with this disorder.

Diagnosis

Studies of HLA antigens may reveal a high proportion of HLA-B5 patients. Histologically, a biopsy specimen from a typical mouth or nasal lesion will show a leukocytoclastic vasculitis with perivascular infiltration that is chiefly lymphocytic.

Treatment

Ulcers of the mouth and nose heal spontaneously and then recur. Local treatment consists of any form of nasal care that prevents dryness, and medicines applied on the mouth to ease oral pain. Corticosteroids are helpful; success has been claimed with azathioprine (Imuran), and the use of chlorambucil has been described. Acyclovir may also be helpful in the treatment of the oral lesions.

Lymphoma-Like Lesions

Polymorphic reticulosis (T-cell lymphoma)

PMR, originally called *lethal midline granuloma* (a clinical term and no longer useful), is also synonymous with lymphomatoid granulomatosis (McDonald et al, 1976).

Clinical features

PMR has a much more rapid course than WG, although it also is characterized by the nasal prodromes of sinusitis and drainage or a lingering cold that worsens. In its earlier stages, however, the destruction is usually unilateral and localized, compared with the usually diffuse bilateral nasal involvement in WG. The lesion is deeply ulcerative and progresses rapidly to involve adjacent sinuses, orbital wall, and palate. The systemic features, present from the onset and tending to progress rapidly, are the same as those in WG except more severe: profound malaise, weakness, migratory arthralgias, and night sweats. Rapid ulceration and necrosis of the local lesion often lead to high spiking fevers and sepsis. However, in a few patients with large lesions there have been few or no systemic features. The patient may present in a toxic, septic, ill state. There usually is unilateral destruction intranasally, with extension to the sinuses and often to the orbit or palate.

Diagnosis

Before biopsy, the investigations described for patients suspected of having WG should be performed. The ACPA test is negative. Comparisons between the two diseases are outlined in Table 40-1 (McDonald, 1990).

Table 40-1. Comparison of Wegener's granulomatosis (WG) and polymorphic reticulosis (PMR)

Feature	WG	PMR
Site		
Upper airway	Diffuse ulceration	Localized, explosive ulcer
Ear	Common	Rare
Orbit	Common	Rare
Trachea	Common	Rare
Lung	Cavitating lesions	Cavitating lesions
Kidney	Nephritis	Mass lesion
Responds to	Immunosuppressives	Radiation
Evolution to true malignancy	No	Sometimes.

Technique of biopsy and special handling of tissue for histochemical study

Diagnosis depends on an adequate biopsy, preferably done in the operating room with either general or cocaine anesthesia and an intravenously administered sedative agent. Many biopsy specimens should be taken from all involved sites; fixed rather than frozen sections should be prepared. In addition, samples should be cultured for fungal and acid-fast organisms, and portions should be "snap-frozen" and stored at -70°C for immunohistochemical and molecular genetic studies (see below). Although PMR usually is not confused with systemic infections, it can be easily confused with malignant lymphoma.

Histopathologic features

The pathologic process consists of a dense infiltrate of cells belonging to the lymphoid family. Mature lymphocytes, plasma cells, histiocytes, and immunoblasts constitute the cell population. Some of the cells show moderate immaturity. The infiltrate has a pronounced tendency toward vascular orientation. For example, it forms an aggregate in the center of vessels and perhaps this accounts for the local infarction of tissue. In turn, this may cause rapid necrosis of the adjacent area that is seen clinically. PMR generally can be distinguished from lymphoma microscopically because there is a mixed population of cells, most of which definitely appear benign and mature. The occasional exception is the presence of various quantities of cells having features of immature lymphocytes and immunoblasts.

Distinguishing PMR from WG is difficult. In general, WG consists of necrotizing granulomas with giant cells and vasculitis, whereas PMR is characterized by an angiocentric pattern of infiltration.

New immunohistochemical techniques

Previously, the tissue removed from the nose of patients suspected of having PMR was cultured to exclude infections by specific organisms that would produce a similar picture. The diagnosis was usually made after dialogue between surgeon and pathologist and the finding of the typical histopathologic pattern described above. More recently, however, immunohistochemical and molecular genetic techniques have allowed a clearer understanding of this disease (Gaulard et al, 1988; Ho et al, 1990; Whittaker et al, 1988). Immunohistochemical studies on biopsy specimens reveal a predominance of T cells with a postthymic (CD2, CD3, CD5+, CD7+) "suppressor-cytotoxic" phenotype (CD8+, CD4-); DNA hybridization demonstrates clonal rearrangements of the beta and gamma T-cell receptor genes. These results indicate that the lymphocyte population in PMR is clonal and they suggest that PMR actually represents an angiocentric T-cell lymphoma.

Treatment

The treatment of choice for localized PMR is a full course of radiotherapy, which is effective. Patients with disseminated disease are treated with a true malignant lymphoma protocol (Pisani and DeRemee, 1990).

Idiopathic midline destructive lesion

I prefer to call this rare disorder IMDD, avoiding the use of the word granuloma, because it is not a granulomatous disease. Tsokos et al (1982) described 11 patients with this disease who were admitted to the Clinical Center of the National Institutes of Health. These patients had destructive lesions of the nasal septum or hard palate. Some had involvement of the skin of the face; in others there was extension into the orbit, nasopharynx, larynx, and trachea. In all patients in this series, the initial biopsy demonstrated a mixture of necrosis and acute and chronic inflammation. Findings of vasculitis or neoplastic lymphocytic patterns were conspicuously absent. The patients in this series were treated with radiation therapy, ranging from 40 to 60 Gy; an objective response to therapy was seen in all patients.

Nasal cocaine abuse mimicking midline destructive diseases

The abuse of cocaine is a global problem with substantial sociologic, psychiatric, and medical repercussions. Nasal use of cocaine is associated with systemic medical complications (hypertension and arrhythmias) and local intranasal complications, of which epistaxis, nasal septal perforation, diminished olfaction, and chronic rhinitis are the most common. When patients are seen with destructive lesions of the nose, with or without perforation of the palate, the possibility of cocaine use should be considered, and the question should be asked (Becker and Hill, 1988; Daggett et al, 1990). In the USA alone, it is believed that there are at least 30 million people who have used cocaine at least once and that about 5 million use it regularly. An incidence of cocaine-induced nasal septal perforation of 4.5% has been reported (Becker and Hill, 1988; Daggett et al, 1990). The actual figure is most likely to be higher. Although I have seen many

cases of chronic rhinitis, with or without small or medium septal perforations associated with cocaine use, I have only seen one case in which the cocaine abuse allowed total destruction of all intranasal structures, including all turbinates and the entire septum, with a large perforation into the hard palate. The patient presented with rhinolalia apperta (with a classic nasal voice). Biopsy showed nonspecific, acute, and chronic inflammation. The palatal lesion was handled with the placement of an obturator, and the septum was closed with two large pieces of 0.20 Silastic. The patient was asked to abstain from cocaine, which she did.

It is important to consider cocaine abuse when patients with intranasal destruction, with or without palatal perforation, are seen.

Differentiation of Churg-Strauss syndrome from Wegener's granulomatosis

A history of asthma and the presence of peripheral blood eosinophilia are rarely found in WG (Specks and DeRemee, 1990). The coagulative or liquefactive necrotizing epithelioid granuloma in WG is morphologically different from the more fibrinoid necrosing epithelioid and eosinophilic granuloma seen in CSS. Clinically, the nasal findings in CSS show allergic rhinitis and polyps; renal involvement in CSS is rare. The nasal manifestations of WG showing the diffuse destructive changes have already been described. In addition, testing for c-ANCA has so far been negative in patients with CSS.

Treatment

CSS responds well to corticosteroid therapy and, as another example of its being different from WG, it does not respond to cyclophosphamide.

Granulomatous Diseases

Sarcoidosis

Sarcoidosis is a chronic systemic granulomatous disease capable of involving almost any organ in the body (Poulter, 1988). It is of immense interest to the otolaryngologist because of its predilection for involving many head and neck organs, including the eye (episcleritis, uveitis), the ear (sudden deafness, unilateral or bilateral facial palsy), the salivary glands (parotid swelling), the mouth (lips, tongue, buccal mucosa, gingiva, hard and soft palates, and floor of nose; these are usually well-circumscribed nodules or papules, occasionally with superficial ulcerations that are brownish red or violaceous), the maxillofacial skeleton (midline bony erosion of the hard palate associated with extensive homogeneous opacification of paranasal sinuses), the larynx (sparing of the vocal cords and a pink-red edematous swelling of the epiglottis), and the trachea (subglottic stenosis). There may be marked cervical adenopathy, hilar adenopathy, tonsillar enlargement, and neurologic involvement (recurrent laryngeal nerve palsies with vocal cord paralysis, either by direct involvement of the cord or by involvement of the neuropathways, including nucleus ambiguous, cranial nerve X, and the superior and recurrent laryngeal nerves, or by mediastinal adenopathy causing compression of the left recurrent laryngeal nerve and vocal

cord paralysis). Other neurologic manifestations include seizures, headache, and optic nerve involvement.

Nasal involvement

Nasal involvement can be external or internal. Externally, sarcoidosis may present as a raised, papular lesion on the nose. Several of these lesions may coalesce to form bluish red swellings. The lesions are firm and elastic when palpated and extend deeply to involve the entire thickness of the dermis.

A form of nasal cutaneous sarcoidosis is called *lupus pernio.* This term was coined by Besnier in 1889 to describe chronic, violaceous cutaneous lesions with a predilection for cold-sensitive areas such as the nose, cheeks, ears, and fingers (Arnold et al, 1990).

Diagnosis

Demonstration of noncaseous granulomas is essential in the diagnosis of sarcoidosis (DeRemee et al, 1980). Usually this information is acquired through sampling of hilar nodes by mediastinoscopy or open lung biopsy. Cultures of biopsy specimens and pulmonary secretions for acid-fast bacilli and fungi are essential. Enthusiasm for the Kveim test is declining in this country. Instead, newer tests such as bronchoalveolar lavage have provided important insights into the pathogenesis of sarcoidosis. Studies suggest that the disease begins in the lung with an alveolitis that consists mainly of T cells. These T cells elaborate chemotactic factors that attract monocytic cells, which ultimately transform into epithelial cells. These cells form the granuloma that potentially leads to fibrosis.

Gallium-67 (67Ga) citrate lung scanning is also useful. 67Ga-labeled citrate is picked up by activated inflammatory cells in the lung and can be detected on scintigraphy. However, this is a nonspecific test.

Serum angiotensin-converting enzyme (SACE) has been shown to be an indicator of activity of sarcoidosis. In a patient with typical symptoms and radiographic and clinical findings of sarcoidosis, hypercalcemia and increased SACE values constitute strong evidence of the presence of sarcoidosis. Again, it must be stressed that the diagnosis should be confirmed by histologic documentation and the exclusion of other causes of noncaseating granuloma.

Other laboratory studies have found that the erythrocyte sedimentation rate is increased. Hypercalcemia and hypercalciuria may occur (10% of the cases). Hypergammaglobulinemia has been noted in 20% to 25% of patients, primarily among blacks. Ten percent of patients with sarcoidosis have increased liver enzyme levels, particularly alkaline phosphatase. Electrocardiographic abnormalities include a prolonged PR interval, bundle-branch block, arrhythmias, and nonspecific ST-segment changes. When sarcoidosis involves leptomeninges, the cerebrospinal fluid contains increased numbers of lymphocytes and increased protein levels.

Immune aspects

Although the cause of sarcoidosis remains unknown, the disease is associated with abnormalities of both cell-mediated and humoral immunity, and the disease develops as a result of an overstimulated local cellular immune response, probably because of an exaggerated T-helper cell network (Specks and DeRemee, 1990). The migration, replication, and interaction of alveolar macrophages, T cells, B cells, and mediators such as interleukin-1, interleukin-2, and type I interferon act in a synergistic manner to produce the migration of monocytes and T cells from the blood to the lung and other parts of the airway, including the nose, and lead to granuloma formation.

Treatment

Treatment of sarcoidosis is controversial, with most of the controversy centering on pulmonary involvement. Ocular involvement responds to cortisone-containing ophthalmic solutions. Involvement of the intranasal mucosa, epiglottis, and subglottis responds to aerosols containing cortisone. In more resistant cases, involvement of these areas responds to brief courses of corticosteroids. Neuropathies, particularly of nerves VII and VIII, should be treated with corticosteroids, to which they usually respond.

In patients with stage 1 pulmonary involvement, treatment is "watchful waiting" with periodic examinations. Seventy percent of patients will have spontaneous remission. Patients in stage 2 or stage 3 who do not show improvement spontaneously or show worsening 6 months after diagnosis should be treated with prednisone (40 mg) on alternate days. The patient is examined in 3 months and the dose is altered according to the response to treatment.

A subset of patients with persistently active or progressive sarcoidosis may be unresponsive to corticosteroids, and, recently, low doses of methotrexate led to improvement in symptoms, chest radiographs, and pulmonary function in a group of patients with progressive pulmonary and extra-pulmonary sarcoidosis.

Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) is classified as a granulomatous vasculitis. It is characterized by the presence of asthma, a history of atopy, and eosinophilia in conjunction with a systemic necrotizing vasculitis (Carrington and Liebow, 1966). It shares many clinical and pathologic features with WG, although CSS rarely leads to renal failure and responds better to corticosteroid therapy. Landham et al use a clinical definition of the syndrome; the diagnosis requires asthma, peripheral eosinophilia in excess of 1.5×10^9/L, and systemic vasculitis involving two or more extrapulmonary organs (Specks and DeRemee, 1990). They note three phases of the disease: (1) a prodromal phase that may persist for years and consists of allergic disease (eg, allergic rhinitis and nasal polyposis, which is frequently followed by asthma); (2) peripheral blood and tissue eosinophilia, chronic eosinophilic pneumonia, or eosinophilic gastroenteritis; and (3) a life-threatening systemic vasculitis.

Histopathologically, polyps removed from the nose show necrosis in association with an eosinophilic exudate, severe fibrinoid collagen alteration, and granuloma formation with accumulation of epithelioid and giant cells that are called allergic granuloma.

Infections

Rhinoscleroma

In 1870 von Hebra coined the term *rhinoscleroma.* The cause was ascribed to a bacteria in 1882. The specific organism has been identified as *Klebsiella rhinoscleromatis.*

Rhinoscleroma is a chronic granulomatous disease of the respiratory tract. Its frequency in the USA is increasing. It was initially described as a lesion involving the nose, but now it is known to involve the larynx, trachea, and bronchi as well.

Nasal involvement

Rhinoscleroma has several distinct stages of development. Initially, there is a catarrhal stage, characterized by foul-smelling purulent rhinorrhea for weeks or months. This is followed by the atrophic stage with large nasal plaques or crusts that are foul-smelling and simulate the lesions in atrophic rhinitis. In the third stage, aptly named the granulomatous stage, multiple granulomatous nodules are found throughout the nose, pharynx, larynx, trachea, or bronchi. These nodules can enlarge and coalesce. During this stage, *K. rhinoscleromatis* is most frequently isolated and the pathologic changes are the most characteristic. Stage 4 consists of fibrosis and stenosis - often complete stenosis of the nostrils. Occasionally, the fibrosis extends to the nasopharynx and trachea.

Diagnosis

Diagnosis depends on high diagnostic acuity and the finding of coalescent, enlarged granulomatous nodules at or near the nasal vestibule, usually diffuse and bilateral. Cultures of infected tissue yield *K. rhinoscleromatis* in 98% of cases; this is diagnostic. Identification of the Mikulicz cell in biopsy specimens is not definitely pathognomonic because this cell can be found (rarely) in other disorders.

Histopathologic features

This is a chronic granulomatous infection with characteristic fibrosis and eosin-staining Russell bodies. The hallmark is the vacuolated Mikulicz cell, a large foamy histocyte that stains well with hematoxylin and eosin. During stage 3, the granulomatous stage, the histopathologic changes are most characteristic and the Mikulicz cell is easiest to identify.

Treatment

Streptomycin (1 g/day for 4 weeks) and tetracycline (2 g/day) is the recommended treatment. A second course of this therapy is repeated after 1 month. Even during the acute or granulomatous stage, this will give a 60% to 70% cure rate. Steroids and radiation therapy are not effective.

In stage 4 of rhinoscleroma, when both nostrils are thickened and stenosed, in addition to antimicrobial therapy, the scar tissue can be "cored out" and the nose can be relined with Silastic (which is removed in 2 to 4 weeks).

Tuberculosis

The increase in the incidence of tuberculosis probably is due to two main factors: the increased number of refugees and the occurrence of tuberculosis infections in patients who have some form of acquired immunodeficiency syndrome. Even in previous years when tuberculosis was common in the USA, involvement of the head and neck was relatively uncommon. As a result, physicians, particularly otolaryngologists - head and neck surgeons, do not suspect tuberculosis, and when the disease involves the head and neck, the diagnosis often is delayed.

Nontuberculous mycobacteria

These types of nontuberculous mycobacteria are often called atypical (McDonald, 1990; Waldman, 1982). They differ from *Mycobacterium tuberculosis* in that they are less virulent, are more likely to infect individuals who have altered host defenses, and are less susceptible to standard antituberculosis drugs. In general, infection with nontuberculous bacteria most commonly represents primary infection. The most common infections caused by these nontuberculous mycobacteria are the following.

1. Corneal ulcers caused by *M. fortuitum.* The pathogenesis is inoculation of the eye by contaminated dust or other foreign material.

2. Cervical lymph nodes infected by nontuberculous mycobacteria. The organisms most commonly responsible for this are *M. scrofulaceum, M. szulgai,* and *M. xenopi.*

Clinical aspects

It is a chronic infection, potentially lifelong, caused by two species of mycobacteria: *M. tuberculosis* and, rarely, *M. bovis.* It almost always is initiated by inhalation of infectious material, rarely by injection, and more rarely still by cutaneous inoculation. Early in the infection, organisms in the bloodstream seek out the lymphatic system and other organs throughout the body, leaving foci that may cause clinical illness after long latency periods. Mycobacteria are acid-fast, nonmotile, weakly gram-positive rods classified in the order Actinomycetales.

Nasal involvement

Nasal tuberculosis, another rare form of the disease, usually affects the anterior septum or anterior part of the turbinates; the nasal floor is spared. Perforations of the cartilaginous portion of the septum occur. In the early stage of the disease, nasal discharge, pain, and partial obstruction are characteristic symptoms. Examination shows a red, nodular thickening, with or without ulceration. The disease has a rapid course, usually resulting in either perforation of the septum or scarring. In lupus vulgaris, an indolent and chronic form of tuberculosis of the nose, scarring is more severe.

Diagnosis

A history of previous tuberculosis or the finding of active pulmonary tuberculosis is extremely helpful in making the diagnosis of tuberculosis of the nose. In the earliest stages, however, the manifestations of nasal bleeding, crusting, or draining may be nonspecific. As in the other granulomatous diseases discussed, diagnosis depends on smears and cultures of acid-fast bacilli and histopathologic examination of an adequate biopsy specimen.

Treatment

Current recommendations include a 2-month course of therapy with three drugs: isoniazid, rifampin, and either streptomycin or ethambutol. After daily therapy for 2 weeks, the drugs may be given twice a week if the patient demonstrates response. Later, twice weekly administration of isoniazid and rifampin is continued for 6 to 7 months. Baseline audiometric and bithermal caloric assessments should be done and repeated periodically because of the ototoxicity of streptomycin.

Histoplasmosis

Although this granulomatous fungal disease primarily involves the larynx and tongue, it can involve any part of the head and neck, including the nose (Darling, 1906; DeMonbreun, 1934; McDonald, 1990).

Epidemiology

Histoplasmosis occurs most often in infants and in elderly people. Although it generally occurs equally in both sexes, elderly men are frequently affected. It has been reported in approximately 30 countries. In the USA it is endemic in the Missouri, Mississippi, and Ohio river valleys where the incidence of past and current infections has reached 85%, as determined by skin testing. Humans and animals are infected by inhalation of the fungus in dust. Soil from chicken houses or from areas contaminated by bat or bird feces is especially rich in *Histoplasma capsulatum* organisms.

Mycology

In its yeast phase the cell is small (3 microm x 5 microm). In the next phase (the mycelial phase), branched hyphae with projections called tuberculate conidia are evident. This is the phase that occurs in the soil. The conidia contain the spores, and humans are infected by inhalation of these spores.

Nasal involvement

Nasal involvement is accompanied by pulmonary involvement and characterized by cough, chest pain, and hoarseness. Chest radiographs show either a diffuse miliary or a localized type of infiltrate. The larynx and tongue are most frequently involved. Nasal involvement consists of either nodules or ulcers composed of masses of organisms in macrophages.

Diagnosis

In addition to positive identification of the organism microscopically, skin tests are useful. One drawback is the high incidence of positive cutaneous responders in endemic areas. The complement-fixation test is reliable because titers persist for long periods; a titer of 1:32 is diagnostic.

Histopathologic features

Microscopically, the lesion is an epithelioid or histiocytic granuloma. The implicated organism can be identified by use of periodic acid-Schiff, Gridley, or Grocott-Gomori methenamine-silver nitrate stain. The capsule is a polysaccharide and stains poorly with hematoxylin and eosin. Organisms can be identified within the granuloma; however, fewer organisms are seen in the presence of a pronounced granulomatous reaction. In these cases, other methods of diagnosis, including culture and serology, are useful.

Treatment

Amphotericin B, in a dose of 1 mg to 10 mg per day and progressing to 1 mg per kg for a total dose of 2 g administered during a 2- to 3-month period, has decreased the mortality rate in the USA to about 50 cases per year.

Rhinosporidiosis

Although this fungal infection is usually seen in Asian and African countries, the disease has been found in the USA for reasons mentioned earlier: more foreign travel and more influx of refugees from Asia (Lasser and Smith, 1976). This disease is caused by *Rhinosporidium seeberi*, which is a funguslike organism not yet successfully grown in culture medium or transferred from a human to an animal host (Lasser and Smith, 1976). The disease is contracted by immersion in contaminated waters in Asia and Africa. Initially, the nasal mucosal lesion is

flat and sessile and then enlarges to become a painless polypoid growth that actually fills the nasal cavities.

Treatment consists of complete surgical excision. No medical treatment has been found to be effective. Microscopically, pseudoepitheliomatous squamous cell metaplasia overlies numerous multisized, microscopic globular cysts called sporangia. In an accompanying granulomatous reaction of fibrous tissue, neutrophils, plasma cells, and lymphocytes are prominent.

Mucormycosis

Mucormycosis is an opportunistic disease that is extremely important to the otolaryngologist - head and neck surgeon. It is caused primarily by fungi of the order Mucorales and of the genera *Mucor, Rhizopus,* and *Absidia* (Eisenberg et al, 1977). Although most commonly seen in patients with poorly controlled brittle diabetes mellitus, it can occur in any patient who is immunosuppressed and who is in a state of metabolic bankruptcy. Initially, there is facial pain, fever, bloody nasal discharge, facial swelling, and edema. The disease progresses dramatically, with facial cellulitis, gangrenous mucosal changes in the nose and paranasal sinuses, obtundation, cranial nerve palsies, vision loss, and proptosis. Sometimes a rapid course leads to intracranial extension and death. Diagnosis is suggested by the combination of a rapidly progressive infection and a black, necrotic mass of tissue filling the nasal cavity, eroding the nasal septum, and extending through the hard palate in an immunocompromised patient.

The finding of broad, nonseptic hyphae (typical of Mucorales) on tissue sections stained with periodic acid-Schiff or Grocott-Gomori methenamine-silver nitrate stain confirms the diagnosis. The prognosis is poor, with a death rate as high as 50% reported.

Amphotericin B is the only effective antifungal drug treatment. Aggressive surgical debridement, when the patient's condition allows it, is also helpful, along with control of the underlying medical disorder.