

**TITLE: Granulomatous Diseases of the Head and Neck**

**SOURCE: Grand Rounds Presentation, UTMB, Dept. of Otolaryngology**

**DATE: October 29, 2003**

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## **INFECTIOUS**

### **Bacterial**

#### ***Cat Scratch Disease and Bacillary Angiomatosis:***

Cat Scratch Disease (CSD) is considered to be the most common cause of chronic benign adenopathy in children and young adults. It is relatively common (0.77-0.86 case per 100,000 population) with an estimated 24,000 cases recognized in the United States per year. The disease is manifested initially by the formation of a small erythematous papule or pustule at the site of inoculation that persists for several weeks. Later, lymph nodes draining the site of infection become enlarged and tender. Patients may also have low grade fevers, malaise and, less commonly, rash, lytic bone lesions, granulomatous conjunctivitis, pneumonitis and CNS involvement. This illness is usually benign and self-limited, lasting 6-12 weeks. History of contact with cats, usually kittens, is found in 90% of patients and antecedent cat scratch in 60%. Risk factors include having a cat in the household less than 12 months of age, especially one with fleas.

#### ***Bacillary angiomatosis***

(BA) is an uncommon vascular proliferative manifestation of infection with *B. henselae* that occurs in patients that are immunosuppressed. Of all reported cases of BA, approximately 90 percent are men that are HIV positive. Manifestations of BA are dermal lesions which can be cutaneous papules, subcutaneous nodules or indurated hyperpigmented plaques. These lesions frequently are friable and may bleed easily; they may also overly an area of bone involvement. Other areas of involvement include the mucus membranes of the mouth, nose, larynx, bronchi and conjunctiva; lung and pleura, bone, and CNS. Visceral involvement is termed peliosis hepatica. The vast majority of CSD is thought to be caused by *Bartonella henselae*, a gram-negative bacillus. CSD occurs in immunocompetent people of all ages; however, 80% of patients are younger than 21 years of age. BA can be caused both by *B. henselae* and *B. quintana*. Risk factors for *B. quintana* infection include homelessness, low income and exposure to lice; risk factors for *B. henselae* infection are similar to CSD including owning a kitten and being

scratched or bitten by a cat. The diagnosis of CSD can be confirmed with serologic testing. A titer of > 1:64 or a fourfold rise is considered positive. The organism is difficult to culture, requiring special media and techniques.

Diagnosis of BA is by demonstration of causative organisms in H and E stained tissue sections; Warthin-Starry stain can also be used. PCR can be used to identify the precise *Bartonella* species. CSD is considered to be a self-limited illness and usually no treatment is required. However, at least one study has suggested that the use of azithromycin for 5 days reduces lymph node size more rapidly than placebo. If the lymphadenopathy is massive (>5 cm), chronic adenopathy may persist for 1-2 years. Aspiration of a suppurated lymph node should be considered to relieve pain and hasten recovery. Formal incision and drainage should not be performed as a draining sinus tract may develop that takes several months to resolve. BA requires treatment. Erythromycin orally is the treatment of choice; the duration depends on the extent of bone or visceral involvement. Extensive or fulminant disease may require intravenous erythromycin. Complete resolution can usually be expected in 3-4 weeks. An alternative antibiotic is doxycycline.

### ***Rhinoscleroma:***

Rhinoscleroma is a rare slowly progressive granulomatous disease of the upper airway which is caused by *Klebsiella rhinoscleromatis*. Most cases diagnosed in this country are in immigrants from endemic areas (Eastern and Central Europe, Central and South America, East Africa and the Indian subcontinent). Airborne disease transmission requires prolonged contact and predisposing factors such as poor nutrition and poor hygiene. This disease invariably involves the nose and may involve the paranasal sinuses, larynx, pharynx and trachea. It progresses through three stages. Catarrhal stage is characterized by prolonged purulent rhinorrhea. Laryngeal manifestations in this stage include hoarseness with interarytenoid hyperemia, exudates and vocal fold edema. In the granulomatous stage, nonspecific symptoms such as epistaxis, nasal obstruction and anosmia are common; rubbery granulomas may present as a nasal mass. In the larynx, glottic and subglottic granulomas may cause airway narrowing and impaired vocal fold mobility. The sclerotic stage is characterized by a dense fibrotic reaction causing extensive nasal scarring, stenosis and deformity. In the larynx, this fibrotic reaction may cause glottic or subglottic stenosis leading to airway obstruction. It is important to note that nasal involvement is nearly universal while paranasal sinus involvement is uncommon. RS can be suspected in those with extensive nasal polyposis adherent to the nasal septum with a lack of paranasal sinus involvement. Cultures of nasal biopsies reveal the organism 50-60% of the time. Surgical debridement and administration of tetracycline or ciprofloxacin for several months are necessary to eradicate disease. Nasal deformity or destruction may require later reconstruction.

### ***Leprosy:***

Leprosy (Hansen's disease) affects the peripheral nerves, skin and upper respiratory system. In lepromatous leprosy, the organisms produce nodular skin lesions and plaques on the feet, hands and ear lobes. Involvement of the nose leads to saddle-nose deformity and upper respiratory disease leads to epistaxis and chronic rhinorrhea. Peripheral nerve involvement is symmetric. Diffuse lepromatous leprosy is diffuse dermal infiltration without focal lesions. Tuberculoid leprosy causes marked and asymmetric involvement of the peripheral nerves with hypopigmented skin lesions. Borderline leprosy has features of both lepromatous and tuberculoid

leprosy. The peripheral neuropathy of leprosy impairs perception of fine touch, temperature and pain which leads to recurrent trauma and ulceration to the extremities. Leprosy is caused by the acid fast bacilli *Mycobacterium leprae*. It is transmitted by nasal droplets and possibly by soil. The disease occurs worldwide in underdeveloped regions of the world. The worldwide number of leprosy cases has fallen from 12 million in 1982 to 6 million in 1991. There are 200 new cases of leprosy diagnosed in the United States per year, most originate in foreign country. The diagnosis is usually clinical. Organisms are infrequently detected in the skin lesions but skin biopsies reveal granulomatous changes with nerve involvement that are consistent with the disease. Depending on whether the disease is lepromatous or tuberculoid, combinations of dapsone, rifampin, minocycline and clofazimine are used. Treatment time is from 2-5 years with the possibility of relapse after cessation of medication.

### ***Nontuberculous Mycobacteria:***

Important pathogenic bacteria in this group are *M. avium* complex, *M. kansasii*, *M. scrofulaceum* and *M. marinum*. *M. avium* is the atypical mycobacterium that most commonly causes disease in humans. This bacterium typically causes pulmonary disease but infection can also result in osteomyelitis, peritonitis, and disseminated disease in patients that are severely immunocompromised. MAC can cause superficial lymphadenitis in children. *M. kansasii* can cause pulmonary disease as well as a disseminated infection with skin lesions such as erythema nodosum, erythema multiforme and induration. *M. scrofulaceum* exists in soil and water and contaminates foodstuffs; it readily colonizes respiratory secretions of adults and children. The most common clinical syndrome associated with this bacterium is lymphadenitis commonly affecting the submandibular area of children less than 12 years old. If left untreated, a draining sinus can form which later calcifies. *M. marinum* generally infects humans as a result of trauma that occurs in water (swimming pools, aquariums, domestic fish tanks, stagnant bodies of water). Typically infection manifests as small papules on the extremities that enlarge, turn blue-purple, and then suppurate and ulcerate. Pulmonary disease results from inhalation of organisms whereas direct inoculation of the organism results in soft tissue disease. MAC and *M. kansasii* are important infections for immunocompromised patients such as those with AIDS or patients undergoing cancer chemotherapy. Identification of mycobacterium in special stains (fluorochrome, Kinyoun, and Ziehl-Neelsen) requires experience. Atypical mycobacteria have very specific culture requirements; detection of growth in culture may take two weeks while identification and speciation may take 2-4 weeks. MAC treatment usually consists of a three drug regimen of Clarithromycin, ethambutol and rifabutin; if the patient is HIV positive then lifelong prophylaxis must be instituted after completion of therapy. *M. kansasii* is difficult to treat and a 3-5 drug regimen must be designed based on sensitivities. *M. scrofulaceum* infection is usually treated by surgical excision of the involved nodes. *M. marinum* treatment consists of rifampin and ethambutol.

### ***Tuberculosis:***

This disease has pulmonary and nonpulmonary manifestations. Extrapulmonary tuberculosis is more likely to affect immunocompromised patients, infants and young children. Extrapulmonary tuberculosis develops when the bacterium overwhelms the immune system and disseminates by way of the lymphatics or bloodstream. Adenitis, especially cervical adenitis (scrofula) is the most common form of extrapulmonary disease. In HIV patients, multiple nodes can be involved. Other important manifestations include otitis media with perforation and

otorrhea, laryngitis. *Mycobacterium tuberculosis* is transmitted by inhalation of bacilli in droplet nuclei. It is estimated that one-third of the world's population is infected with TB. The incidence of tuberculosis in the United States is quite low; case rates are high in HIV-infected patients, the homeless, recent immigrants from high-prevalence countries and intravenous drug users. PPD test is usually positive in those infected with tuberculosis; however, this may be negative in immunocompromised patients. Sputum stains and cultures should reveal the organism. Extrapulmonary TB can be diagnosed by positive blood culture or biopsy. Several drugs are used to treat tuberculosis in adults and children including ethambutol, isoniazid, rifampin, pyrazinamide and streptomycin. There are multiple second-line treatments. Number and type of drugs used and duration of therapy depend on multiple factors including organism sensitivities, side effects of the medications and drug allergy.

### ***Actinomycosis:***

Actinomycosis accounts for three major clinical syndromes: cervicofacial disease, abdominal disease and thoracic disease. Only cervicofacial disease will be discussed here. Cervicofacial disease is usually subsequent to gingival manipulation or intraoral trauma. Most commonly, the perimandibular region is affected with soft tissue swelling, abscess or mass lesion. Other cervicofacial manifestations of actinomycosis are periapical dental infections, sinusitis and other soft tissue infections of the head and neck including, salivary glands, thyroid, external ear and temporal bone. The organisms that cause actinomycosis usually grow as saprophytes in the mouth. Disruption of the mucosal barrier is necessary for the initial establishment of infection. After infection is established it can spread contiguously, hematogenously or be aspirated causing pulmonary involvement. Muscle and bone involvement are due to direct spread. Sinuses can develop which drain to the skin or adjacent cavities. Pus characteristically contains "sulfur granules" which can be seen wither micro- or macroscopically. *Actinomyces* are microaerophilic/anaerobic filamentous gram-positive rods. Suspect this disease when space-occupying lesions are combined with pus-draining sinus formation and soft tissue/bone involvement. *Actinomyces* can be identified by gram stain. Anaerobic processing of culture specimens is required. Antibiotic treatment with either penicillin G or ampicillin is required combined with surgical management as indicated. Clindamycin may also be used.

### ***Syphilis:***

Syphilis infection proceeds in three stages. Primary syphilis is manifest as a painless ulcer (chancre) at the site of inoculation which appears after about three weeks. Secondary syphilis occurs 3-6 weeks after the resolution of primary syphilis and is usually manifest as a diffuse, nonpruritic macular rash which affects the palms and soles. Other manifestations of secondary syphilis include condyloma lata, mucus patches which are slightly raised, grayish ulcerations on the mucus membranes and patchy alopecia. At this stage, patients may also have syphilitic meningitis, optic neuritis, iritis and uveitis. Tertiary disease occurs 5-25 years after initial infection and cardiovascular syphilis, neurosyphilis and gummatous syphilis. Congenital syphilis is acquired transplacentally or contact with an infectious lesion during delivery. Symptoms of early congenital syphilis include: osteochondritis and periostitis, snuffles, maculopapular rash, condyloma lata, anemia, low birth weight, hepatosplenomegaly and fever. Manifestations of late congenital syphilis include dental abnormalities, poorly developed maxilla, high palatal arch, saddle nose, frontal bossing and interstitial keratitis. Syphilis is caused by the microaerophilic spirochete *Treponema pallidum*. It is a sexually transmitted disease which

is transmitted by contact with mucocutaneous lesions or transplacentally. Risk factors are unsafe sexual practices, multiple sex partners and drug abuse. The incidence of all stages of syphilis has declined since 1991. The number of new cases of primary and secondary syphilis in the United States in 1997 was 8,500 (3.2 cases per 100,000). The incidence of congenital syphilis in the same year was 27 cases/100,000 live births. Serologic tests are used to diagnose syphilis. Screening tests include VDRL and RPR. Dark field microscopy can be performed on carefully collected specimens from a suspected syphilitic lesion. Primary syphilis and secondary syphilis can both be treated with one time I.M. dose of benzathine penicillin. Tertiary syphilis is also treated with penicillin with regimen depending on the manifestation.

## **Fungal Infections**

### ***Histoplasmosis:***

*Histoplasma capsulatum* is a dimorphic fungi that causes disease after inhalation of the organism in soil enriched with bird, chicken or bat excrement. It can cause a wide spectrum of disease depending on the patients immunologic status and number of inhaled organisms. Most commonly, infection is asymptomatic. Other manifestations are acute primary histoplasmosis (a pulmonary infection associated with fever, malaise, cough, chest pain which can be severe), chronic pulmonary histoplasmosis (progressive focal consolidation and cavitation of lung parenchyma), and disseminated histoplasmosis (usually occurring in immunocompromised individuals with protean manifestations). Two other important disease syndromes are mediastinal granulomatosis and fibrosing mediastinitis. Mediastinal granulomatosis occurs as a result of the granulomatous inflammatory response elicited by *H. capsulatum*. The mediastinal lymph nodes coalesce and form large lesions in the mediastinum which may invade or compress nearby structures such as the bronchi, trachea and esophagus. Symptoms may include cough, dysphagia, odynophagia, formation of esophagopulmonary fistula and the development of post-obstructive pneumonia or bronchiectasis. Fibrosing mediastinitis results when the healing process is complicated by a hyperintense fibrotic reaction culminating in a relentless progressive invasion of mediastinal structures. Fibrosing mediastinitis due to histoplasmosis is the most common cause other than malignancy of superior vena cava syndrome. HIV infected patients may present with an acute syndrome including septic shock, meningitis, oropharyngeal ulcers and cutaneous lesions. Five hundred thousand people in the United States become infected each year; risk factors include living in the Ohio or Mississippi River valleys, living in an endemic region, cave exploration, excavation, cleaning chicken coops, or other activities that involve disturbing soil enriched with this organism. Diagnosis is usually established with histopathological examination at which time the organism can be detected with special stains such as Grocott silver stain or Wright-Giemsa stain. Cultures can be sent and new blood culturing techniques such as lysis centrifugation method have improved yield. Amphotericin B is the drug of choice in immunocompromised patients and those with life-threatening disease. Itraconazole can be used for non-life-threatening disease.

### **Blastomycosis:**

*Blastomyces dermatitidis* is a dimorphic fungus that lives in moist soil. The major route of transmission to humans is via inhalation of airborne spores; disease manifestations are usually pulmonary. Extrapulmonary blastomycosis of the skin typically occurs in conjunction with pulmonary infection and results from hematogenous dissemination; primary cutaneous

blastomycosis can occur after dog bite, inoculation in the lab or during autopsy. Two types of skin lesions are noted: verrucous or ulcerative. Lesions typically affect exposed skin but mucocutaneous lesions can occur. Blastomycosis may also affect the skeleton, central nervous system or involve multiple visceral organs as in disseminated disease in the AIDS patient. Risk factors for disease include living in endemic areas such as the Ohio or Mississippi River valley and exposure to dust from construction or excavation in these areas. Diagnosis is made by the identification of the organism in tissue, exudates, or histopathologic sections. Treatment of life-threatening infection is with amphotericin B; those with non-life-threatening disease can be treated with itraconazole.

### ***Coccidiomycosis:***

*Coccidiodes immitis* is a fungus that lives in the soil in dry desert climates. Infection occurs after inhalation of the arthroconidia. Infection is frequently asymptomatic. The disease syndrome most commonly associated with *C. immitis* infection is pneumonia. Frequently pulmonary disease will be associated with erythema nodosum or erythema multiforme. Complications of severe disease include large pulmonary cavitations, bronchopleural fistula, severe hemoptysis, and meningitis. Other manifestations such as granulomatous skin lesions, subcutaneous abscess, septic arthritis, and osteomyelitis are infrequently encountered. Risk factors include exposure to dust especially in the summer and fall. Endemic areas are southern California, southern Nevada, southern New Mexico and parts of Texas. Earthquakes and dust storms increase incidence. There are approximately 100,000 cases of coccidiomycosis diagnosed annually in the United States. This disease is diagnosed via skin test or culture. Cultures grow readily (2-5 days) and are confirmed via a DNA probe. Laboratory personnel should be informed if coccidiomycosis is suspected as arthrospores readily become airborne and may be inhaled. Treatment is via amphotericin B or one of the azoles.

### ***Candidiasis:***

There are over 150 species of *Candida*. The majority of candida infections are endogenous and result from immune-suppression and prolonged use of broad spectrum antibiotics. Candida esophagitis may result if nausea, odynophagia, substernal chest pain and vomiting. Physical exam of patients with esophageal candidiasis may not yield the diagnosis; concurrent oral thrush may be present. Diagnosis can be suggested by barium swallow (shaggy-appearing mucosa with possible nodules and cobblestoning). Endoscopy is the preferred method of diagnosis. Complications relate to deep invasion and inflammation and include stricture and rarely esophageal perforation. Topical therapy as for oral thrush is usually adequate; those with severe disease or immunocompromise may require systemic therapy. Oral thrush is characterized by creamy white, curdlike patches on the tongue and other oral mucosal surfaces. These patches are removable and leave a raw, bleeding and painful surface. Diagnosis is via characteristic clinical picture. Demonstration of the organism on KOH or other special stain strongly supports the diagnosis. Culture of the organism from oral scrapings is not high yield as this organism may be part of the normal flora of the oral cavity. Nystatin suspension or clotrimazole troches are effective therapy. Topical antifungal creams will treat angular cheilitis. Systemic therapy may be used in those with severe infection or immunosuppression. Itraconazole or fluconazole may be used.

### ***Rhinospordiosis:***

Rhinospordiosis is an infection of the nasal, palatal or conjunctival mucus membranes. It leads to indolent, painless, friable polypoid excrescences. It is endemic in South India and Sri Lanka. It is extremely rare in the United States. The causative organism is *Rhinospordium seeberi*. Treatment is by excision.

### ***Aspergillosis and Phycomycosis:***

*Aspergillus* is a ubiquitous mold with some species causing disease in humans; most commonly: *A. fumigatus*, *A. flavus*, and *A. niger*. Disease can be categorized as hypersensitivity lung diseases (extrinsic asthma, extrinsic allergic alveolitis, allergic bronchopulmonary aspergillosis), noninvasive aspergillosis (aspergilloma), and invasive aspergillosis (lung, sinus, CNS, other organ systems). Predisposing factors for invasive infection include: granulocytopenia, AIDS, prolonged corticosteroid or cytotoxic therapy, bone marrow transplantation, hematologic malignancy, diabetes mellitus, and liver failure. Aspergilloma (aka mycetoma, fungus ball) of the lung develops in patients with pre-existing cavitary lung disease. It is heavy aspergillus colonization of a preexisting cavity. It can cause hemoptysis which may be severe enough to warrant lobectomy. Aspergilloma may also develop in the paranasal sinuses. Persistent pain and discharge are common symptoms. Invasive aspergillosis may occur in immunosuppressed patients. Signs of invasive disease in the sinuses include: headache, toothache, nasal congestion, purulent nasal discharge, sinus or eye pain. Ptosis and loss of extraocular eye movements indicate extensive invasion into the orbit. If invasive aspergillus sinusitis is suspected, rigid nasal endoscopy should be performed and well as aspiration of sinus contents to evaluate for fungal elements. CT scanning can detect extent of involvement. *Pseudallescheria boydii* is a fungus that is morphologically similar to *Aspergillus* sp. It causes similar disease such as fungus ball and invasive sinusitis. It has a propensity to cause infection of the globe after trauma. It is important to differentiate *P. boydii* from *Aspergillus* sp. as *P. boydii* is resistant to amphotericin B and only responds to intravenous miconazole which has significant toxicities. Mucormycosis is caused by molds from the family Mucorales: *Rhizopus*, *Rhizomucor*, *Mucor*, *Absidia*, *Cunninghamella*. These agents are ubiquitous in nature. Infection is via inhalation of organisms in an appropriate host. Rhinocerebral mucormycosis occurs most commonly in patients with uncontrolled diabetes, especially during or after an episode of ketoacidosis. It may also occur in patients with prolonged neutropenia and occasionally in organ transplant recipients. The first symptoms are facial pain, headache and nasal stuffiness. As the disease progresses, orbital pain and facial anesthesia may develop. Visual changes occur after invasion of the orbit. Mental status changes are noted with penetration into the brain with ensuing cavernous sinus thrombosis, carotid artery thrombosis, or cerebral abscess formation. Two thirds of patients are comatose at the time of first clinical examination. Physical findings include proptosis, loss of extraocular movements, drainage of black pus from the eye, black necrotic tissue in the nasal cavity or a black eschar on the hard palate. Imaging with CT or MRI is essential and surgical debridement and initiation of amphotericin B is urgent. Correction of underlying predisposing factors is critical. If left untreated, rhinocerebral mucormycosis is fatal within a week of onset. After appropriate therapy, the survival rate in diabetics with rhinocerebral mucormycosis is 50 percent.

## **Parasites:**

### ***Leishmaniasis:***

The bite of a sandfly inoculated with one of multiple *Leishmania* species causes this disease. The disease manifests as one of three syndromes: visceral (kala-azar), cutaneous, and mucocutaneous (Espundia). Cutaneous leishmaniasis begins as a papule at the site of inoculation; this progresses to ulcer formation. Most forms of this disease heal spontaneously in three months. 90% of cutaneous leishmaniasis occurs in Afghanistan, Brazil, Iran, Saudi Arabia, and Syria. Mucocutaneous leishmaniasis involves the mucosal membranes of the nose and mouth; it may lead to epistaxis or nasal obstruction or septal perforation. Treatment is with stibogluconate or stibogluconate and interferon gamma. Aspiration and punch biopsy of the leading edge of a cutaneous or mucocutaneous lesion are the best techniques to gather specimens for culture and histology. Most cases of leishmaniasis in the United States are imported by those who have been exposed in endemic countries such as military personnel, Peace Corps workers or ornithologists. It is also observed in those who live or work at the forest edge; rural settlers, farmers clearing forests and road construction workers in endemic areas are at risk. New World cutaneous and mucocutaneous leishmaniasis is found from South Texas to northern Argentina.

### ***Myiasis:***

This is infestation with maggots from the larvae of screw worms or bot flies. Furuncular myiasis results from human bot fly larvae carried on mosquitoes in Central and South America; these larvae are deposited on the patient's skin when the mosquito ingests a blood meal. When the larvae hatch, they penetrate the skin. Furuncular myiasis results in a characteristic pustular lesion with a central breathing pore that emits bubbles under water. Surgical excision may be required. Creeping dermal myiasis results when the eggs of the horse botfly come in contact with bare skin. The larvae penetrate the skin but do not mature. For weeks, they migrate in the epidermis resulting in a serpiginous pruritic rash. Larvae may be removed from beneath the skin with a needle. Draining wounds attract many species of flies. The larvae enter wounds where they penetrate skin and produce large suppurative cavities. Larvae may also infest normal body cavities such as the mouth, nose, ears, sinuses and eyes. Surgical removal is usually required.

## **Trauma**

### ***Intubation Granuloma:***

These almost invariably involve the vocal process of the arytenoids. The initial trauma progresses from a contact ulcer to a granuloma to a pedunculated polyp. Patients may report hoarseness and foreign body sensation. Treatment is by voice rest, surgery.

### ***Teflon Granuloma:***

A known complication of Teflon injection for treatment of unilateral true vocal cord paralysis is an overzealous granulomatous response causing increasing dysphonia and even airway obstruction. This granulomatous reaction infiltrates into surrounding tissue and makes resection of the granuloma and reconstruction of the defect difficult.

## **Neoplastic**

### **Langerhans Cell Histiocytosis:**

This disease entity has historically been termed Histiocytosis X or Langerhans Cell Granulomatosis. Current terminology favors Langerhans Cell Histiocytosis. To add to confusion, this disease has been grouped into various subsets such as eosinophilic granuloma, Hand-Schuller-Christian disease and Letterer-Siwe disease. These subsets are no longer recognized as such. Langerhans Cell Histiocytosis is one disease with a broad spectrum of presentations and varied course. LCH lesions are a proliferation of Langerhans cells usually accompanied by multinucleated giant cells and eosinophils. The Langerhans cell can be identified on electron microscopy by the presence of Birbeck granules in the cytoplasm. This is usually a pediatric disease but can be diagnosed in adults. The incidence of LCH in the United States has been estimated at 0.05 to 0.5 cases per 100,000 children per year. The etiology is unclear; it is believed that there is a genetic predisposition to this disease. Bone, skin and lung lesions are common but LCH lesions have been reported in the palatal mucosa, thymus, nose, larynx, hypothalamus, thyroid, gastrointestinal tract, lymph nodes, parotid gland, kidney, and CNS.

Head and neck involvement is very common. Flat bones are affected more commonly than long bones and in the head and neck the skull is frequently affected with the temporal bone less often affected. Temporal bone involvement may present as persistent otitis media with dermatitis of the external auditory canal or external ear. Dental manifestations are also common with hypertrophic gingivitis and underlying jaw LCH with loose teeth. Lymph node involvement is uncommon but cervical lymph nodes are most commonly involved and this may be massive. Orbital masses can produce proptosis. Unexplained rash may be the presenting complaint. Damage to the hypothalamic-pituitary axis can lead to diabetes insipidus, growth retardation and hypothyroidism.

Most observers believe this is a nonneoplastic disease. The course of the disease is variable with spontaneous resolution or visceral dissemination with compromise of vital organs leading to death. Treatment ranges from observation to low dose steroids, low-dose radiation or curettage. Chemotherapy is employed with some success for young patients with a fulminant course. A recent study defined three risk groups: older patients without organ dysfunction are the good risk group who are likely to have spontaneous resolution without therapy, patients under 2 years of age without organ dysfunction were the intermediate risk group, and patients less than 2 years of age with organ dysfunction were the poor risk group with a survival of less than 50%.

### **Lobular Capillary Hemangioma(Pyogenic Granuloma):**

This condition is neither infectious or granulomatous. This is a common benign vascular lesion of skin that is friable and prone to bleeding. The exact etiology is unknown but may be influenced by hormonal milieu or local trauma. Treatment is excision or destruction of lesion via curettage. Recurrence is common. Oral cavity lesions that occur during pregnancy are termed pregnancy tumor and are likely to resolve after parturition.

### **Necrotizing Sialometaplasia:**

This disorder is a benign, self-limited reactive inflammatory process that involves salivary glands. It can follow trauma and is more common in smokers. It begins as a submucosal swelling usually at the junction of the hard and soft palate. It progresses to yield an ulcerative lesion that usually is less than 3 centimeters in greatest diameter. The chief importance of this lesion is the occasional difficulty in distinguishing necrotizing sialometaplasia from squamous cell carcinoma and mucoepidermoid carcinoma. Obtaining an adequate biopsy specimen is important. No therapy is warranted as the process is self-limiting.

## **Inflammatory Disease of Unknown Etiology**

### **Sarcoidosis:**

This disease is a multiorgan disorder with a variable clinical picture. The etiology is unknown but likely represents a genetic predisposition combined with an environmental trigger. Sarcoidosis typically strikes young adults less than 40 years old; there is a slight female preponderance. African Americans are frequently affected and have more severe manifestation than whites. Two patterns of disease have been described: acute sarcoidosis with a sudden onset usually undergoing spontaneous remission within two years and chronic sarcoidosis with a gradual onset, organ-specific symptoms and tendency to symptomatic relapse. Constitutional symptoms are frequent. Organ-specific manifestations include pulmonary involvement in 90% of patients; pulmonary symptoms only occur in 30-50% of patients and include dyspnea, dry cough and chest pain. Pulmonary findings include hilar adenopathy and parenchymal infiltrates. Enlarged peripheral lymph nodes are common. Cutaneous lesions range from small purple papules and subcutaneous nodules to lupus pernio (bluish discoloration of the nose, cheeks, lips or ears). Sarcoidosis can also be associated with erythema nodosum. Ocular sarcoid occurs in 20-30% of cases, most commonly chronic uveitis but may affect the lacrimal gland as well. Cardiac, liver and renal involvement occur uncommonly.

Diagnostic criteria include:

1. compatible clinical and radiographic findings,
2. histologic finding of noncaseating granulomas,
3. exclusion of other diseases with similar findings or local sarcoid reaction.

Diagnosis is usually made via transbronchial lung biopsy combined with bronchoalveolar lavage findings of elevated CD4/CD8 ratio, biopsy of other sites including peripheral lymph nodes, skin lesions, and minor salivary glands of the lip. Otolaryngologic manifestations of sarcoidosis occur in 10 to 15 % of patients; rarely, these are the presenting symptoms. Cervical adenopathy is frequently present; biopsy by FNA has a high yield in making the diagnosis. Parotid involvement is present in 6% of patients and is usually bilateral; biopsy (FNA) of the affected glands can confirm the diagnosis. Sinonasal manifestations occur in 1-4% of patients and can include nasal obstruction, postnasal drip, headache and recurrent sinus infection. Physical exam reveals dry, friable mucosal lesions of the septum and inferior turbinates with thick discharge and crusting. Granulomatous infiltration can also result in subcutaneous, yellowish nodules; less commonly, polypoid mucosa may be present. Septal perforations and even saddle nose deformity may result. Aggressive lesions may cause erosion of the soft or hard

palate. Treatment for nasal symptoms may include saline nasal irrigation, topical and systemic steroids; the role of surgery has been debated but recent reports have demonstrated that surgical management is safe and effective to provide symptomatic relief of nasal obstruction or recurrent/chronic sinusitis in selected patients. Cranial neuropathies are uncommon but the most commonly affected cranial nerve is the facial nerve. Heerfordt's disease is facial nerve paralysis in association with parotid swelling. Sarcoidosis affects the larynx in 0.5 to 8.3 % of patients. The characteristic appearance on laryngoscopy is pale, boggy edema of the epiglottis, AE folds, arytenoids and false vocal cords. Sarcoidosis may involve the oropharynx with tonsillar hypertrophy causing upper airway obstruction and sleep apnea; granulomatous lesions in the pharynx and esophagus may lead to fibrosis and stenosis. Treatment of sarcoidosis is with steroids or immune suppressants.

### **Idiopathic Midline Destructive Disease:**

This disorder is also known as lethal midline granuloma. It is a rare spectrum of lymphoproliferative disorders causing destruction of nose, paranasal sinuses, palate and facial soft tissues. Currently, most cases of IMDD are attributed to lymphoma. Controversy exists as to whether all cases of IMDD are not either frank lymphoma or a lymphoproliferative disorder that will evolve into lymphoma. Treatment is with radiation therapy.

## **Autoimmune/Vasculitic Diseases**

### **Wegener's Granulomatosis:**

Wegener's granulomatosis is an idiopathic disease believed to be immunologically mediated. The incidence of Wegener's granulomatosis is estimated at 1-3 cases per million. It affects males and females equally with the average age at diagnosis 20-40 years. Wegener's almost exclusively affects the white population. This disorder classically is associated with the triad of pulmonary, renal and head and neck manifestations. However, a wide spectrum of organ systems may be involved or only one organ system may be involved. Head and neck complaints are the most common manifestations of this disease at presentation followed by pulmonary, joint, orbital and renal involvement. Pulmonary disease typically manifests as cavitating granulomatous lesions with hemoptysis, cough and dyspnea. Renal involvement typically takes the form of progressive renal failure with hematuria, proteinuria and red cell casts found on urinalysis. The nose and paranasal sinuses are the most frequently affected sites in the head and neck. Clinical findings range from mild nasal obstruction and pain over the nasal dorsum to total nasal collapse. Patients may complain of foul-smelling rhinorrhea, epistaxis, hyposmia or epiphora. The nasal exam classically reveals nasal crusting, mucosal inflammation, granulation tissue, and evidence of sinusitis. Perforation of the nasal septum is relatively common; a saddle nose deformity results in 10-25% of those patients with nasal involvement. Chronic sinusitis is a frequent manifestation and occurs in approximately 50% of those with nasal involvement. Oral cavity involvement is rare with nonspecific deep ulceration of the oral and oropharyngeal mucosa occurring in 2-6% of patients. Ocular and orbital involvement is very common and may be the only manifestation of disease. Common ocular symptoms include proptosis, pain, diplopia, visual loss and periorbital cellulitis. Orbital inflammatory changes in WG are usually bilateral and can either represent an extension of nasal and ethmoidal disease or can be a discrete inflammatory orbital mass. Subglottic stenosis occurs in 9-16% of patients and can involve just

the immediate subglottis or extend for 3-4 centimeters. Tracheostomy will be required by 50% of those with laryngeal disease. Otologic involvement occurs in 19-38% of cases and most commonly manifests as otitis media with effusion. This is likely secondary to Eustachian tube obstruction resulting from luminal granulomata or nasopharyngeal inflammation. Chronic suppurative otitis media is present in 24% of patients with WG. Sensorineural hearing loss occurs with a reported frequency of 8%. Making the diagnosis involves testing for serum ANCA and tissue biopsy. These need to be used in combination as both tests can lack diagnostic sensitivity. The site of biopsy affects the diagnostic yield with paranasal sinus biopsy offering the highest yield. Biopsy sites should be generous and include clinically unaffected tissue. If WG is strongly suspected, serum ANCA and tissue biopsies may have to be repeated at intervals to establish the diagnosis. A positive cANCA is specific for WG; a positive pANCA is a nonspecific finding in a vasculitis workup. Treatment involves the use of various regimens on corticosteroids and immunosuppressive medications. A multidisciplinary approach should be used with the inclusion of an otolaryngologist, rheumatologist, nephrologist, pulmonologist and ophthalmologist.

### **Relapsing Polychondritis:**

This is a rare immunologically mediated disease with many otolaryngologic manifestation. Patients produce antibodies to type II collagen. Affected cartilagenous structures include ears, nose, joints and tracheobronchial tree. The estimated annual incidence of RP is 3.5 cases per million. Average age at diagnosis is 44 to 51 years. Auricular exam in acute exacerbation may reveal red, swollen and tender external ear with sparing of the lobule. The skin of the helix assumes a violaceous hue. This may subside spontaneously over days to weeks. Repeated attacks leave the external ear droopy. The external auditory canal and the Eustachian tube can become narrowed by edema or collapse. This can be complicated by otitis media. Nasal chondritis may lead to destruction of the nasal cartilage leading to saddle nose deformity and a flat nasal tip. Fifty percent of patients with RP have laryngotracheal disease. Symptoms may include dyspnea, wheezing, choking, hoarseness, and tenderness over the thyroid and anterior tracheal cartilage. Inflammatory damage to the cartilage and subsequent collapse can lead to dynamic obstruction. Tracheostomy may be life-saving in these patients. Ocular manifestations are common with the most common syndromes being episcleritis, scleritis and conjunctivitis. Other findings may be proptosis, periorbital lid edema and chemosis. Effective treatment regimens have not been standardized as this disease is quite rare.

### **Systemic Lupus Erythematosus:**

SLE is a relatively common autoimmune disorder affecting nine women for every one man. It usually strikes women of childbearing age. This disorder has protean manifestations: photosensitive skin eruptions, serositis, pneumonitis, myocarditis, nephritis, and CNS involvement. The head and neck manifestations of this disorder are predominantly cutaneous and mucosal lesions. A malar rash ("butterfly rash") is the initial sign in 50% of those affected. Mucosal ulcerations are seen in the oral cavity. Patients with well established disease have a 3-5% rate of ulceration or perforation of the nasal septum. Laryngotracheal manifestations are uncommon but include true vocal fold thickening or paralysis, cricoarytenoid arthritis and subglottic stenosis. Dysphagia is a common symptom. Neuropathy may affect cranial nerves in 15% of cases. Discoid lupus erythematosus is a subtype of SLE in which cutaneous lesions

predominate without visceral involvement. These lesions involve the face in 85 % of cases. Lesions are well-demarcated, erythematous, edematous papules that depigment and scar on resolution.

### **Sjogren's Syndrome:**

SS is a chronic autoimmune disorder affecting predominantly the salivary and lacrimal glands. Exocrinopathy is associated with dense lymphocytic infiltrates of glandular tissues and B cell hyperreactivity with various serum autoantibodies that underscore its nature as an autoimmune disease. 90% of patients are women; the disease usually affects individuals in the fourth and fifth decades of their life. The prevalence is estimated at 1 to 3 % of the general population. When only lacrimal and salivary glands are affected, the disease is called primary SS or sicca syndrome. When this disorder occurs in combination with another connective tissue disease, it is termed secondary SS. Xerostomia is the predominant oral symptom of patients with salivary gland involvement. This can affect chewing and swallowing and cause sore mouth, dental caries, dysphagia and fissures of the tongue and lips. The tongue is typically smooth with fissures and atrophy of the filiform papillae. Major salivary gland enlargement occurs in 25 to 66 % of patients with primary SS but does not occur in secondary SS. Xerophthalmia is the major manifestation of lacrimal gland involvement which may lead to chronic irritation and destruction of the corneal and bulbar conjunctival epithelium. Patients may report a sandy feeling, itchiness, or burning sensation. Additionally, patients may report they are unable to tolerate smoke, air drafts or light. Extraglandular manifestations include arthralgias and myalgias, dry cough and dyspnea, chronic atrophic gastritis, primary biliary cirrhosis, Raynaud's phenomenon, small vessel vasculitis, peripheral neuropathy and various cutaneous lesions. The diagnosis of SS can be made with a combination of serological testing (SS-A, SS-B), biopsy of labial salivary glands to evaluate the number of mononuclear aggregates, Schirmer's test, and sialography demonstrating sialectasia. Patients with SS have a 44 times greater risk of developing non-Hodgkin's lymphoma than the general population. Patients should be monitored for persistent unilateral or bilateral parotid gland enlargement, splenomegaly, lymphadenopathy or type II mixed monoclonal cryoglobulinemia as these may be signs of the development of a lymphoma. Patients should also be screened for other connective tissue diseases, especially rheumatoid arthritis, systemic lupus erythematosus, scleroderma and primary biliary cirrhosis. Patients should be instructed on oral hygiene. Xerophthalmia may be managed with commercially available eye lubricants. Salivary secretagogues can be administered as long as they are not medically contraindicated. Saliva substitutes can also be used.

### **Churg-Strauss Syndrome:**

CSS is a rare autoimmune syndrome of diffuse vasculitis that is almost universally associated with severe asthma. Patients with this disease may show necrotizing eosinophilic vasculitis affecting nearly all major organ systems usually preceded by the development of asthma. The cause of CSS is unknown but may be related to exposure of a genetically susceptible patient to a foreign inhaled antigen, causing rhinosinusitis and asthma. Blood and tissue eosinophilia result which can lead to eosinophilic pneumonia or gastroenteritis. Vascular inflammation may also result and affect multiple organ systems. Asthma treatments have been implicated in the development of CSS especially the leukotriene inhibitors and the withdrawal of corticosteroids. No set of standard diagnostic criteria exist but the following triad has been

suggested: 1. a history of asthma; 2. blood eosinophilia over 1500 cells per microliter; 3. systemic vasculitis involving two or more organs. The initial presenting symptom is usually rhinitis. Other associations include recurrent sinusitis, nasal polyps and nasal obstruction. Pulmonary involvement is almost universal with asthma which is difficult to manage, pulmonary infiltrates or pleural effusions. Other prominently involved organ systems are: peripheral nervous system with mononeuritis multiplex, gastrointestinal system with abdominal pain and possible intestinal perforation, cardiovascular system with endomyocarditis and coronary vasculitis, skin lesions which are variable, and renal involvement. Systemic symptoms are prominent. The diagnosis of CSS should be considered in patients with asthma if there is either a significantly raised peripheral eosinophil count or pulmonary infiltrates. Treatment is with corticosteroids with the possible addition of cyclophosphamide. The prognosis is good with appropriate therapy.

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