Introduction

The term “granuloma” is derived from the Latin “granulum”, referring to a small particle such as a grain. Granulomatous diseases have plagued humans for millennia, with evidence of tuberculosis infection in Egyptian mummies and descriptions of the disease in Hippocrates’ writings. Syphilis has also been said to have been described by Hippocrates, and was recognized as a venereal disease in the fifteenth century. The minute granules of disseminated mycobacteria deposited in host tissues were noted in the seventeenth century. A French physician, Jean Jacques Marget, likened these granules to millet seeds and coined the term “miliary”. In the nineteenth century Robert Koch developed a method of staining and identifying bacteria, and was able to differentiate infectious and non-infectious granulomatous diseases. Actinomyces was isolated in vivo and associated with sulfur granule production in the late nineteenth century by Dr. Bergey. The advent of modern pathology, with improved microscopes, staining techniques, and communication between researchers spawned this new category of “granulomatous diseases” in the early twentieth century. The diagnosis and treatment of these diseases continues to evolve to this day, and perhaps due to their relative scarcity, continue to create a diagnostic dilemma to physicians of every specialty. All of these diseases have manifestations in the head and neck, and many patients initially present to the otolaryngologist. Therefore a keen understanding of the manifestations, workup, and subsequent treatment of these conditions is essential to every practicing otolaryngologist.

Pathophysiology

Neutrophils usually remove agents that incite acute inflammatory responses by phagocytosis and digestion. However, if an agent is indigestible, yet provokes an acute response, this would lead to a vicious cycle that would deplete the body’s white count, and cause severe damage to local normal tissues. The body deals with such indigestible substances and prolonged inflammatory reactions by forming granulomas.
The principal cells involved in granulomatous inflammation are macrophages and lymphocytes. Macrophages are much longer lived than neutrophils, and can phagocytose an indigestible agent, thus keeping it from provoking an acute immune response. Upon phagocytosis of an indigestible substance, macrophages lose their motility and accumulate at the site of injury, where they undergo a structural change to become epithelioid cells. These cells are larger and have more abundant pale cytoplasm, causing them to resemble epithelial cells. Nodular collections of these epithelioid cells form the heart of the granuloma. These cells often become surrounded by collections of lymphocytes, and contain multinucleated giant cells, formed by the fusion of up to fifty macrophages. When the nuclei of these cells is arranged in a horseshoe pattern, the cell is named a “Langhans Giant cell”. When a pathogen, such as a fungal spore or silica particle, is found within the giant cell, the cell is named a “foreign body giant cell”. Other inflammatory cells may be associated with the granuloma as well.

Granulomatous disorders usually present either as a nonhealing ulcer, or as a persistent mass. A fine needle biopsy is performed, and the pathologist often reports acute and chronic inflammation. As the differential diagnosis in this case is quite extensive, the physician must follow up with a thorough history and repeat physical examination. It is important to establish first whether this lesion represents an isolated disease process, or is a manifestation of a systemic illness.

The history should make special reference to fever, night sweats, weight loss, loss of appetite, malaise, arthralgias, and other indicators of chronic disease. Travel history and risks for immunosuppression, such as sexual behavior and certain medications, are also of importance. Physical examination should include a directed search for hepatosplenomegaly or lymphadenopathy in the inguinal, axillary, or cervical regions. If the first biopsy is inconclusive or inadequate for culture, excisional biopsy is warranted. Discussion with the pathologist intraoperatively may aide in submission of appropriate specimens. Laboratory tests should be ordered at this point, including an ANA, CBC, ESR, and urinalysis. Further laboratory workup should be directed as the patient’s symptoms dictate. A CXR is also included in the initial workup if the patient’s has systemic symptoms. Early consultation with a rheumatologist and infectious disease specialist is highly recommended. An accurate diagnosis is mandatory because the spectrum of treatment ranges from antibiotics to radiation and chemotherapy, which, if prescribed inappropriately, may exacerbate the patient’s condition.

**Infectious Etiologies – Fungal**

*Histoplasmata capsulatum* causes a relatively common fungal infection in the United States. It is endemic to the central portion of the United States, more specifically the Mississippi and Ohio River Valleys. Typically, inoculation with the spores does not cause any clinical consequences; however, symptomatic infections can occur. Acute infection is transmitted by inhalation of fungal spores. The usual course of disease includes fever, headache, chills, myalgia, fatigue, chest pain on deep inspiration, coryza, sore throat, and occasional gastrointestinal
symptoms. Physical examination is usually unremarkable, but a routine chest x-ray will often show small scattered infiltrates and hilar lymphadenopathy. The infection will resolve spontaneously, or progress into a chronic disseminated disease. In the chronic disseminated form of histoplasmosis, constitutional symptoms of weight loss, fever, fatigue, and fever predominate. 

ENT symptoms include dysphagia, sore throat, hoarseness, painful mastication and gingival irritation. Granulomatous lesions may also appear on the lips, gingiva, tongue, pharynx, and larynx. The lesions appear as firm, painful ulcers, with “heaped-up” margins. They may also have a verrucous appearance and mimic carcinoma. Approximately 40-75% of adults with disseminated disease present with oropharyngeal involvement, in comparison to only 18% in children.

Diagnosis requires taking swab specimen or biopsy from the center of an ulcerative lesion and culture on Sabourad's medium. Amphotericin B continues to be the treatment of choice, but newer less toxic antifungal agents are currently being tested.

**Blastomycosis dermatitidis** is found mainly in the southeast, central and mid-Atlantic regions of the United States, with the prevalence of reported infection far less than that of *Histoplasma capsulatum*. The typical patient is male (10:1 male/female) in the age group of 20 to 69 years of age. The infection is usually asymptomatic, and the patient usually is not ever aware that he has been inoculated. However, acute and/or chronic symptomatic disease may arise in susceptible patients. Constitutional symptoms predominate with disseminated disease. Manifestations range from pneumonitis to cutaneous, osseous, and genitourinary involvement. Cutaneous lesions are proliferative and verrucous like, with subsequent scarring. Upper aerodigestive tract involvement is much less common than in histoplasmosis. However, the larynx and hypopharynx may be involved, showing areas of erythematous hyperplasia on examination. Fibrosis of the cords may occur as the disease progresses, with pharyngocutaneous fistula formation as a late clinical feature. Chest x-ray will be abnormal in 75% of the cases, demonstrating obvious nodular infiltrates. Diagnosis is by sputum culture and microscopic examination of skin scrapings. Treatment is amphotericin B.

**Phycomycosis (a.k.a. mucormycosis)** is an opportunistic fungal infection affecting immunocompromised patients (poorly controlled diabetic, hematologic malignancy, transplant patient, etc.). *Mucor* sp., *Rhizopus* sp., and *Absidia* sp. comprise the group of fungi causing this disease. They are ubiquitous in the environment. This disease entity is initially localized, with rapidly advancing locoregional spread which is rapidly fatal. The most common complaint is facial pain, but patients may also present with bloody rhinorrhea, fever, or facial edema. These symptoms rapidly progress to diplopia, obtundation, and death in as little as 24 hours. Mortality rates have been reported as high as ninety percent after cranial neuropathies are noted. Physical examination may reveal facial edema, tenderness to palpation of the face, cranial nerve dysfunction, proptosis, reduced ocular motion, and chemosis. In addition, examination of the mucous membranes (especially the middle turbinate) may reveal black eschar overlying areas of frank necrosis. Diagnosis entails microscopic examination of mucosa excised at bedside. The fungal hyphae are described as broad and sparsely septate, and invasion of the tissue will be noted. Computerized tomography is used to determine the overall extent of disease. Treatment is
demands emergent and aggressive craniofacial debridement of necrotic tissue with orbital exenteration as needed. Amphotericin B pharmacotherapy is also indicated.

*Aspergillus fumigatus* is also ubiquitous in the environment. Transmission is by inhalation of the spores.

Those individuals with an underlying pulmonary disease such as COPD, may harbor a chronic infection with long standing cough and often hemoptysis as a complaint. Pulmonary cavitation containing a ball composed of hyphae (coined aspergilloma) may occur. There is an invasive form of aspergillosis, but it is generally contained within an immunocompromised patient population. Regarding head and neck manifestations, the non-invasive form of the disease usually involves a single sinus cavity with symptoms of thick, dark nasal secretions, and fullness as presenting complaints. This may progress to form a fibrosing, granulomatous inflammatory reaction in an involved sinus. In the invasive form of the disease, patients may present with facial hypesthesia, proptosis, ophthalmoplegia, and possible visual loss. Diagnosis is by microscopic examination of the secretions, in addition to a culture. The hyphae may be differentiated from other fungi (especially mucormycosis group) by their morphology- septate, bifurcating hyphae. Computerized tomography will demonstrate sinus pathology, frequently with calcifications and inhomogenous sinus density in both acute and chronic forms of the disease. Treatment is surgical excision of the involved tissue, and if invasion is evident, treatment with Amphotericin B. The allergic fungal entity is out of the scope of this discussion.

*Candida albicans*, also a usually harmless organism, can cause life threatening infections in the immunocompromised. The typical presentation is the creamy white pseudomembrane that covers the mucus membranes of the oral pharynx and oral cavity. Symptoms include severe odynophagia, dysphagia, laryngitis, and angular cheilitis. Diagnosis is made by swab and culture, and treatment is initially with nystatin, and systemic antifungals for more severe or persistent disease.

*Rhinosporidium seeberi* is prominent in Southern India and Sri Lanka, but is extremely uncommon in North America. Travel history is of obvious importance. The mucous membranes of the nose, conjunctiva, and palate are the most common sites of involvement. The lesions are painless, but polypoid, friable, and erythematous ("strawberry lesions"). Treatment consists of excision of the lesion.

*Coccidioides immitis* and *Cryptococcus neoformans* may cause granulomatous type inflammatory reactions; however, they rarely affect the head and neck regions.

**Infectious Etiologies – Parasitic**

*Leishmaniasis* (caused by *Leishmania sp.*) presents as four distinct clinical pictures—(1) visceral leshmaniasis a.k.a. kala azar, (2) cutaneous leshmaniasis (new world vs. old), (3) mucocutaneous leshmaniasis a.k.a. espundia, and (4) diffuse cutaneous leshmaniasis. These parasites are transmitted from an animal reservoir to humans via an insect vector, the sandfly. Of the clinical forms, the new world cutaneous and mucocutaneous tend to have more involvement in
the head and neck regions. The new world cutaneous form is caused by *Leishmania mexicana*. Following a bite from the infected fly, 1-3 cm well-demarcated papules are found at the inoculum sites. Ulceration of the lesions occurs later. These generally resolve spontaneously without treatment or adverse sequelae within 6 months. As an exception, however, primary lesions of the ear may, for unknown reasons, persist for years, causing extensive destruction of the pinna and surrounding structures. Biopsy of the lesion is required for diagnosis. Treatment of the more persistent infection requires Pentostam (sodium antimony gluconate) parenterally for at least 20 days. *Leishmania braziliensis* causes the mucocutaneous form of leishmaniasis, primarily found in Central and South America (except Chile and Argentina). Following the sandfly bite on an extremity (usually lower), several lesions appear that undergo extensive ulceration. Hematogenous spread may occur, typically involving the mucous membranes of the oral cavity and nasopharynx. Progressive inflammation and destruction of tissue of the mouth and nose occurs months to years later. Diagnosis is based on biopsy, while treatment consists of Pentostam for at least 30 days. Serological tests exist which allow the early diagnosis of relapse by detecting a rising antibody titer via a direct agglutination test.

*Myiasis* refers to an infection with the larvae (maggots) of the common screw-worm fly. Infection occurs when the fly deposits the larvae in an open wound, or when the itself may invades normal tissue or else enters through the mouth, ears, or nose. In the U.S., the most common form of myiasis is furuncular. A pruritic furuncular type lesion forms in the area that the larva has penetrated the skin, which later develops into a non-healing papule. From this papule, larva may be found to emerge. In a second clinical variant of myiasis, a nonfuruncular lesion is typically found in the nasopharynx. Geographically, this type is generally found in the Orient. Diagnosis is made by microscopic examination. Treatment is surgical opening of the lesions and removal of the larvae.

*Toxoplasma gondii* causes infection via ingestion of contaminated cat feces, or poorly cooked infested lamb or pork. Most patients ward of this infection without symptoms, although the parasite may affect any organ system including the CNS. It most frequently presents in the head and neck region as a persistent neck mass. Pyremethimine and trisulfapyrimidines are the anti-parasitics of choice.

**Infectious Etiologies – Bacterial**

Disease caused by *Mycobacterium tuberculosis* is well studied and provides an excellent example of the granulomatous inflammatory process. The disease is spread from person to person by inhalation of an airborne droplet containing the organism. In the overwhelming majority of patients, the primary infection is asymptomatic; however, inoculation initiates an inflammatory response with a cell mediated hypersensitivity component developing over time. It is this immune response that sequesters the tubercle bacilli and prevents further multiplication or spread. The healing process then occurs, often leaving a calcified granuloma. A ghon complex, seen radiographically, refers to the peripheral lung granuloma which has become calcified in conjunction with a calcified hilar lymph node. Most patients undergo complete resolution of the initial infection; however, in approximately 5% of those exposed, a symptomatic, clinical state
occurs when there is inadequate containment of the organism. Some may develop symptoms shortly after the initial infection, while others develop disease years later, where the bacilli have been in a dormant state. The clinical manifestations of tuberculosis are extensive, but pulmonary disease is usually an integral component.

Regarding head and neck involvement, cervical lymphadenopathy (referred to as scrofula) is the most common. The lymph nodes are multiple, matted, and non-tender, with usual bilateral involvement of the posterior triangles of the neck in adults, or of the submandibular triangle in children. The larynx is involved in approximately 1% of patients who have active pulmonary tuberculosis, with bronchogenic spread as the most likely mechanism for infection. Specifically, the arytenoids are involved with greatest frequency, followed by the true vocal cord, epiglottis, false cord, and subglottic area.

The lesions may be edematous, granulomatous, or ulcerated; however, on biopsy sections, a tuberculoma is usually found. In a patient with laryngeal involvement, the symptoms include cough, hoarseness, and weakened voice. Oral cavity lesions are found in .05 to 1.5 % of the patients with evidence of pulmonary disease. The lesions may present in several forms, either painful or painless, single or multiple, and as fissures, nodules, plaques, vesicles, or ulcers. The tongue has the greatest incidence of involvement (approx. 50%) in those with oral involvement. The gingiva, buccal folds, and dental sockets may also be sites for lesions. Salivary glands may also be involved, usually secondary to oral cavity infection. Typically, the patient presents with diffuse enlargement of the parotid gland. Although far less common than other head and neck sites, otologic involvement may be found, usually in the clinical form of multiple tympanic membrane perforations. A thin, watery otorrhea may also be present. In addition, a mastoiditis may ensue as the disease progresses.

Diagnosis requires asking about constitutional symptoms, a positive PPD, an abnormal chest X-ray, and sputum showing acid fast bacilli. An excisional biopsy of a lymph node may also be warranted for diagnostic purposes. Treatment requires the use of multiple anti-tuberculosis agents for a period of 9-12 months depending on the sensitivity of the organism and the nature of the infection. A tympanomastoidectomy may be required for otologic complications, and lymph node excision may be indicated for chronically draining, fluctuant nodes. It should be noted that lymph node excision may lead to a chronically draining cutaneous fistula through previously unaffected skin.

Nontuberculosis mycobacterial infections may also present as granulomatous lesions in the head and neck region. Included in the group of non-TB mycobacterium are M. kansaii, M. scrofulaceum, M. avium- intracellulairis, M. gordonii, and M. fortuitum. Transmission appears to be from soil to mouth or eye. Children are most frequently infected with corneal ulceration in the head and neck region. Following ocular involvement is cervical lymphadenopathy (scrofula), typically unilateral within the anterior cervical, preauricular, and submandibular regions. The lymph nodes are discrete, separate, and may progress into an abscess. Diagnosis is made by excisional biopsy of the involved lymph node with acid fast bacilli culture. Acid fast staining of the sample for bacilli will give the presumptive diagnosis. Treatment consists of antibiotics (i.e.
isoniazid, rifampin, ethambutol, sulfonamide, fluoroquinolones) that are sensitive for the particular organism.

*Mycobacterium leprae* is the organism that causes leprosy (Hansen's disease), a chronic granulomatous infection which involves superficial tissues such as skin and peripheral nerves. Epidemiologically, the disease is far more prevalent in tropical climates and is transmitted from human to human through open, weeping ulcers, nasal secretions, and breast milk. There appears to be a spectrum of disease, ranging from a tuberculoid form to a lepromatous form. The tuberculoid form is characterized by massive involvement of peripheral nerves resulting in severe pain and muscle atrophy. Involvement of the facial nerve may occur, albeit rarely, that may result in exposure keratitis and corneal ulceration.

In contrast, the lepromatous form of leprosy has widespread skin lesions, typically hypopigmented, concave macules with ill defined borders. Centrally, the lesion is indurated and convex. There may also be neurologic involvement, but cutaneous disease is more pronounced. Early symptoms with lepromatous leprosy include nasal stuffiness, epistaxis, and hoarseness, which relate to mucosal nodules in the nose (especially anterior inferior turbinate) and laryngeal ulcerations. The mucosal lesions may progress to septal perforation with subsequent nasal collapse and saddle nose deformity. The skin lesions of leprosy show a predilection for cheeks, nose, brow, and ear. Lateral loss of the eyebrow is a common finding. The involved skin in the face and forehead regions may become corrugated and thickened late in the course of disease, resulting in a leonine facies. Diagnosis is by skin scrapings, which on culture and staining demonstrate the organism. Biopsy of skin lesions is also indicated. Dapsone is the usual course of therapy; however, resistance to this medication has become an increasing problem. Other agents used in treatment include rifampin, clofazimine, ethionamide, and quinolones. Vaccination with Bacillus Calmette-Guerin (BCG) in endemic areas continues despite conflicting clinical results and modest efficacy.

Cat-Scratch Disease is caused by one of two intracellular, gram negative bacilli, *Rochalimae henselae*, or *Afipia felis*, which require special staining (Warthin-Starry) for detection. Cat exposure, with scratch or bite, is identified in a large number of cases. The disease is found mainly in children --90% under the age of 18. Clinically, a primary lesion, vesicular, papular or pustular, is seen at the site of inoculation, followed by regional lymphadenitis. Additionally, in 38-73% of studied cases, cervical lymphadenopathy is also seen. Systemic complaints of fatigue, malaise, and low grade fever may co-exist. Diagnosis is based on history of exposure, the presence of a primary inoculation site, absence of other causes for lymphadenopathy, and histological findings (suppurative and necrotizing granulomatous lymphadenitis with stellate abscesses) on biopsied lymph nodes. This disease is self-limited and disappearance of the lymphadenopathy in one to two months is the rule. Treatment is generally supportive, with incision and drainage of necrotic lymph nodes only in cases of severe abscess formation. Curettage is preferred over excision if vital structures are at risk. Bacillary Angiomatosis, a recently recognized entity, is also caused by the same bacteria. It occurs predominantly in young adults as cutaneous papules or subcutaneous nodules. *Rochalimae quintana* is also believed to
cause some of these infections. Immunocompromise is the primary risk factor, followed by exposure to cats. The histopathology consists of vascular (lobular capillary) proliferation with pleomorphic gram negative bacilli. Both of these diseases tend to respond to erythromycins, doxycycline, and rifampin. Bacillary angiomatosis differs from cat scratch in that if it is left untreated it is progressive and often fatal.

**Actinomycosis** is an indolent suppurative infection caused by an anaerobic or microaerophilic organism. Infection follows after aspiration of the *Actinomyces* organism into the lung, or contact of the organism with damaged mucosa (i.e. poor dental hygiene, dental abscess). Pathologically, the agent grows in characteristic grains. The infectious process is walled off by the granulomatous inflammatory process with extensive fibrosis demonstrated on histological studies. Cervicofacial actinomycosis typically presents as a red, indurated, non tender subcutaneous mass in the anterior cervical triangle or submandibular region. The overlying skin may have a purplish discoloration. There may be several draining sinuses present (61% of patients). In addition, 57-89% of patients report fever, while other symptoms include weight loss, malaise, nausea, vomiting, and sweating. Demonstration of characteristic sulfur granules on microscopic examination provides the diagnosis with confirmation by culture. Treatment consists of oral penicillin or tetracycline for 2-4 months (mild cases) or 6 weeks of parenteral penicillin g (severe cases). Surgical debridement of necrotic tissue may be necessary to facilitate recovery.

**Syphilis**, caused by the spirochete *Treponema pallidum*, may present with several manifestations in the head and neck area, each correlating with a specific stage of the disease. In the primary stage, a painless ulcer (chancre) exists at the site of inoculum. Although this is generally found in the genital area, it may manifest in the head and neck region, more specifically, involving the lips, tonsils, or tongue. Reactive lymphadenopathy is also found. This generally resolves spontaneously and is followed by a secondary stage 6 months later, where widespread mucocutaneous lesions predominate. These lesions may appear as white macules or papules, and, histologically, are found to contain the organism admixed with dense infiltrates of plasma cells and lymphocytes. These lesions are extremely contagious. Other symptoms include acute rhinitis, pharyngitis, laryngitis, and otitis media. In addition, there may be loss of eyelashes and localized alopecia. As in the primary stage, the secondary stage resolves spontaneously and a latent stage is entered.

The tertiary stage of syphilis develops in 1/3 of these patients, while 1/3 undergo spontaneous remission after the second stage, and the remaining 1/3 have latent disease for life. The characteristic lesion of tertiary syphilis is the gumma, which is a lesion containing nodules of plasma cells, lymphocytes, epithelioid cells, and fibroblasts. Nasoseptal perforation (resulting in saddle nose deformity), and hard palate perforations occur commonly. Laryngeal involvement includes a diffuse, gummatous nodular infiltrate. Ulcerations of the larynx may also occur with chondritis or perichondritis occurring when there is secondary bacterial invasion. The temporal bone may also be affected in syphilis, particularly when the gummatous lesion causes an obliteratorative endarteritis. Due to the reduced blood supply, the bony labyrinth necroses, followed by gradual loss of the membranous labyrinth. The patient may present with hearing loss.
(sensorineural --sudden, bilateral, fluctuating, with poor speech discrimination scores) and/or vertigo. In addition, there may be a frank osteomyelitis of the temporal bone. Congenitally acquired syphilis has its own set of clinical manifestations. This may include a saddle nose deformity, frontal bossing, short maxilla, Hutchinson's incisors, mulberry molars, mental retardation, and sensorineural hearing loss. Approximately 40-50% of these children also present with meningitic disease.

Diagnosis consists of darkfield microscopy on non-oral lesions (oral flora may resemble T. pallidum) and the use of serological testing, namely VDRL and FTA-ABS. The VDRL is used as a screening test but is not specific for syphilis. A positive VDRL is confirmed with the FTA-ABS, which is more specific. The FTA-ABS remains positive for many years following infection, whether or not the patient is treated. Treatment consists of penicillin or tetracycline (allergic patients), while steroids may be used to reduce otologic symptoms.

*Klebsiella rhinoscleromatis* causes rhinoscleroma, which has three distinct phases: (1) catarrhal stage—prolonged purulent rhinorrhea (honeycombed color), (2) granulomatous stage—characterized by small, nodular masses in the upper airway which later coalesce, and (3) sclerotic stage—dense fibrosis that causes stenosis of the nose, larynx, and tracheobronchial tree. Epidemiologically, this organism is found in Central America and Eastern Europe. Demonstrating the existence of the organism in vacuolated histiocytes (Mikulicz’s cells) can be useful for diagnosis. Treatment is with streptomycin or tetracycline. Patients with significant stenosis may require dilatation procedures.

Granuloma inguinale, anthrax, brucellosis, and tularemia are other, less commonly observed infectious, granulomatous diseases that may involve the head and neck.

**Traumatic Etiologies**

Post-intubation granulomas of the larynx are relatively uncommon, with several studies showing widely disparate rates of occurrence. It occurs almost exclusively in the adult population and for unknown reasons women are involved more frequently (75% of documented cases). In the majority of cases, the lesion is situated on the vocal process of the arytenoid cartilage. Mucosal abrasion form the tube initiates the sequence of events including perichondritis followed by secondary infection. A contact ulcer may form with ensuing granuloma formation. The lesion may be sessile or pedunculated. The patient may complain of voice alteration (hoarseness, breathy voice) or even dyspnea with the larger lesions. Indirect laryngoscopy supplemented with an flexible endoscopic examination is needed for diagnosis. Treatment may be observational, instructing the patient on voice rest and the use of antibiotics for secondary infections, or may warrant surgical excision for the pedunculated lesions.

Pyogenic granuloma is typically seen as a response to minor trauma with a secondary bacterial invasion. It is a misnomer in that it is not a true granulomatous infection, rather granulation tissue that forms following an inciting traumatic event. Generally, these are painless, soft lesions that are found along the gingiva. Grossly, they may appear to be elevated,
pedunculated, or sessile and tend to bleed easily if traumatized. Treatment is surgical excision for those lesions that are particularity symptomatic.

Reparative granuloma has an unknown etiology, but is likely due to local trauma such as tooth extraction. The peripheral form is usually a pedunculated, mucosa covered red/blue mass arising from the gingiva or alveolar mucosa. It is most commonly seen on the anterior aspect of the mandible. The central form is endosteal in nature, and is most commonly anterior to the first molar in the mandible. Radiographically the lesion appears as a lytic, expansile mass, with well-demarcated nonsclerotic margins, and an intact but thinned bony cortex. Treatment is curettage and recurrence is common.

Foreign Body Etiologies

The urate crystals in gout incite granulomatous lesions as they are deposited in the tissues. Histologically, the crystals are surrounded by a fibroblasts, plasma cells, macrophages, and foreign body giant cells. The resulting lesion is referred to as a tophi. The tophaceous deposits occur throughout the body, but classically involve the helix or antihelix of the ear. Tophi may ulcerate and extrude a material that is rich in monosodium urate crystals. Examination under polarizing microscopy for urate crystals aids in distinguishing this from other causes of subcutaneous nodules. Gout also produces an arthritis type picture since the crystals are capable of inciting a significant inflammatory response within the joint space. Usually the joints of the lower extremities are affected, but there have been reports of involvement of the cricoarytenoid joint. Symptoms from this involvement include throat pain, hoarseness, and dysphonia. Chronic inflammation of the joint space may result in fixation of the arytenoid cartilages. Gout is treated medically, using colchicine or indomethacin for acute attacks, and allopurinol for prophylaxis.

Cholesterol granulomas are usually found in the pneumatized area of the temporal bone or the paranasal sinuses. For these granulomas to form, there is a predisposing lack of aeration to the site. Cholesterol precipitates in the areas of cell breakdown (erythrocytes, mucosa) with a resulting foreign body reaction. Regarding temporal bone involvement, the patient may be asymptomatic or may have symptoms related to CN V-VIII dysfunction when the cerebellopontine angle is involved in the expansile lesion. Cholesteatomas may also be found in association with cholesterol granulomas, where the clinical symptoms are more likely to be related to the cholesteatoma. Paranasal sinus involvement also occurs. The patient may complain of nasal congestion, rhinorrhea, facial pain, and possibly ophthalmological complaints if there is ocular extension. Most lesions in the sinus, however, do not expand or cause erosion of the bony walls. Diagnosis is made by CT scan which shows a smooth walled lesion, whether in the temporal bone or sinus cavity, which is isodense to brain tissue. The cholesterol granulomas are surgically drained, and aeration is re-established.

Topical nasal usage of cocaine may produce ulcerative granulomas which erode the nasal septum, soft palate and/or nasopharyngeal mucosa. Staph aureus propagates the ulcer in most cases. Treatment is gram positive antibiotics, and cessation of cocaine use.
Neoplastic Etiologies

**Eosinophilic granuloma** presents as a bony lesion, usually involving the flat bones of the skull (i.e. frontal, temporal, mandible). It is characterized by a localized collection of histiocytes (polygonal and in sheets) eosinophils that cause resorption of bone, producing a radiolucent lesion. Patients are generally children and young adults. This disease process is considered the localized form of histiocytosis X. Treatment is surgical excision with radiation therapy used for recurrent lesions.

**Hand-Schuller-Christian disease** is considered to be a chronic, disseminated form of histiocytosis X. The presence of sheets of polygonal histiocytes admixed with eosinophils, plasma cells, and lymphocytes is the characteristic microscopic finding in the lesions. Again, this tends to be a disease of children and young adults. Typically, there are several bony lesions present (polyostotic), abdominal viscera involvement, and cutaneous lesions (poor prognostic sign). In addition, there is triad that exists in approximately 10% of the patients, consisting of bone lesions, diabetes insipidus, and exophthalmos. The diagnosis is made on biopsy. Treatment plans differ--consisting of pharmacological (vinblastine and corticosteroids) to radiation therapy. Despite treatment, the mortality rate approximates 30%.

**Letterer-Siwe** is a disease of infants that consists of hepatosplenomegaly, lymphadenopathy, bleeding diathesis, anemia, cutaneous lesions, and generalized hyperplasia of macrophages in a variety of organs. This is the acute disseminated form of histiocytosis X. The temporal bone may be involved, with ear pain and/or otorrhea (18% - 61%) as a clinical symptom. Treatment consists of chemotherapeutic agents, but the disease is uniformly fatal in 1-2 years.

**Benign fibrous histiocytoma** most often develops as a painless mass in sun-exposed and orbital tissues. It has also been found in the salivary glands, and the deep layers of the scalp and face. It occurs more commonly in males and can occur at any age. The histopathology consists of a biphasic cell population of fibroblasts and histiocytes with spindle shaped cells and elongated nuclei arranged in a “storiform”, or cartwheel pattern. The malignant variant differs with malignant pleomorphic sarcomatous cells, bizarre giant cells, increased number of mitoses, and tendency for local invasion. Treatment of the benign disease is local excision with clear margins.

**Necrotizing sialometaplasia** may be found wherever salivary tissue is present, but is most commonly found in the oral cavity at the junction of the hard and soft palate. The lesion is a deep and sharply demarcated ulcer, but may be preceded by a small indurated mass. The pathology is characterized by metaplastic epithelial cells lining small salivary ducts with preservation of lobular architecture. This preservation of architecture differentiates the lesion from squamous cell and mucoepidermoid carcinoma, for which it may be easily confused by the unsuspecting pathologist. The lesion resolves spontaneously within two to three months, and does not need excision unless the mass effect is interfering with deglutition or dentures.

**Polymorphic reticulosis, lethal midline granuloma, and lymphomatoid granulomatosis, angiocentric lymphoma,** are synonymous terms used previously to describe a condition that is now
believed to be a type of peripheral T-cell lymphoma (angiocentric lymphoma). Histopathologically, it differs from conventional lymphoma in that it is comprised of a polymorphic rather than a monomorphic infiltrate. Clinically it differs in that it occurs in extranodal tissues (lungs, CNS, skin, kidneys). The disease is more common in males, with a peak incidence in the fifth decade of life. The initial presentation may be as benign as nasal congestion with clear rhinorrhea; however, the patient's condition rapidly deteriorates as the involved structures necrose as a result of vascular compromise. Destruction of the external nose, nasal cavity, soft palate, hard palate, and nasopharynx progresses in an unrelenting fashion. High spiking fevers and sepsis frequently occur. Death occurs from hemorrhage, secondary infection, and/or cachexia. Systemic features are also present, consisting of profound malaise, night sweats, migratory arthralgia, and weakness. The disease may become disseminated with involvement of central nervous system, gastrointestinal tract, and the lungs. Pulmonary related complaints consist of cough, chest pain, and hemoptysis. Cutaneous involvement is almost always present--seen as a maculopapular rash that progresses to an ulcerated lesion. Diagnosis of polymorphic reticulosis is made by biopsy and immunohistochemical staining and processing. It is important to differentiate the disease of polymorphic reticulosis from Wegner's granulomatosis, as the presentation and examination may have some significant similarities. Differences exist, however, that should allow accurate diagnosis. For instance, histological examination of the lesions in Wegener's disease are necrotizing granulomas with giant cells and vasculitis, whereas the polymorphic reticulosis lesion shows angiocentric infiltration of atypical polymorphonuclear cells. In addition, the use of laboratory methods for detecting anti-neutrophil cytoplasmic antibodies (ANCA) is helpful in diagnosing Wegener's. Although recurrence of disease is possible, localized disease may be effectively treated with external beam radiation therapy, with debridement of necrotic tissue as needed. Multiregional disease may be treated with cyclophosphamide and prednisone, while diffuse systemic disease is treated with a larger armament of chemotherapeutic agents. The overall mortality rate is 50 - 70%.

Unknown Etiologies

Sarcoidosis is a chronic disease characterized by the accumulation of non-caseating epithelioid granulomas, affecting many organ systems. The etiology is uncertain, with the prevalence of disease in the United States ranging from 10-40 per 100,000 (17:1 black:white ration). It generally occurs during the third to fifth decade, with a gender preference for females. Manifestations of the disease become apparent when the normal architecture of the involved tissue becomes distorted by the sarcoid granulomas. The lung, lymph nodes, skin, and eye are most common organs affected, and to lesser extent, other head and neck structures. Approximately 90% of individuals with sarcoidosis have an abnormal chest x-ray, while only 50% of these patients will actually have evidence of permanent lung disease. Dyspnea and a dry cough are common complaints. Lymphadenopathy is also a common finding, affecting 75 - 90% of patients. Intrathoracic lymph node groups are predominately involved; however, cervical lymph nodes (non-tender, non-adherent, rubbery, and firm) may also be appreciated. Skin manifestations (in 25% of the patients) include erythema nodosum, plaques, maculopapular eruptions, subcutaneous nodules, or lupus pernio. The manifestation of lupus pernio is seen as an indurated blue-purple,
shiny, swollen lesion with predilection for the nose, cheeks, ears. Additionally, skin plaques and maculopapular eruptions typically involve the facial structures.

Regarding ophthalmological manifestations (25% incidence), the patient may present with uveitis and episcleritis. Although cervical lymphadenopathy is the most prevalent abnormality in sarcoidosis, parotid gland involvement is present in approximately 10% of the studied cases. Bilateral parotid gland involvement is the rule. The parotid glands on physical examination are non-tender, firm, and smooth. In 5% of the cases, the larynx, supraglottic, may demonstrate an erythematous, edematous, nodular, and non-ulcerated mucosa, with airway obstruction as a symptom. Diagnosis of sarcoidosis requires a combination of radiographic, clinical, and histologic positive findings. Common findings from laboratory evidence includes hypergammaglobulinemia on serum protein electrophoresis, elevated liver functions tests (transaminases), elevated serum calcium on electrolyte panel, and an elevated erythrocyte sedimentation rate. Angiotensin converting enzyme is also elevated in 80-90% of the patients and is helpful in diagnosis as well as monitoring disease status. Prednisone, or other immunosuppressive agents are used for treatment.

Autoimmune and Vasculitic Disease

Wegener's Granulomatosis is a systemic disease, thought to be autoimmune, characterized by vasculitis and predominantly epithelioid necrotizing granulomas in the involved tissue. Typically, the patient has a triad of necrotizing granulomas of the upper airway and lungs (cavitating lesions), renal involvement (focal necrotizing glomerulonephritis) and disseminated vasculitis. The patient may present with widely varying symptomatology, but complaints of nasal obstruction, bloody rhinorrhea, nasal crusting, and nasal pain are the most common. On examination, the mucosa of the nasal cavity is ulcerated with possible perforation of the nasal septum (especially posterior surface of the vomer). Otologic involvement occurs in 20-25% of the cases with serous otitis media and possible sensorineural hearing loss related to cochlear vasculitis, while tracheal manifestations may be stridor from subglottic involvement. Diagnosis is based on biopsy of the nasal mucosa displaying granuloma formation and vasculitic involvement of the small arteries. Laboratory evaluation should include a standard chemistry panel (BUN/Creatinine), sedimentation rate, rheumatoid factor, and anti-neutrophil cytoplasmic antibodies. ANCA is found in approximately 90% of those with Wegener's disease, more specifically, the c-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibodies) variant. A chest X-ray is also indicated. Treatment for limited, mild forms of Wegener's has responded well to trimethoprim-sulfamethoxazole (unknown mechanism of action), while the more severe forms require immunosuppressive therapy of corticosteroids, cyclophosphamide, and immuran.

Systemic lupus erythematosus is a disease in which tissues are damaged by deposition of autoantibodies and immune complexes. There is a definite gender predilection with women being affected in 90% of the studied cases. Black females in child bearing age comprise the largest group of those affected by this disease. The prevalence is approximately 15-50 per 100,000 in the United States. There is an exceedingly large number of manifestations of the disease, but malar rash (50% incidence), oral ulceration (40% incidence), polyarthritis (60% incidence), and arthralgia (95% incidence) are some of the more common. Laryngeal involvement may include a
chondritis/perichondritis, diffuse thickening of the vocal cords, and arthritic involvement of the cricoarytenoid and/or cricothyroid joints. The patient may complain of hoarseness, dysphonia, pain, and possibly obstruction. In addition, the patient may have nasal cavity involvement, examination revealing anterior septal perforations. Discoid lupus erythematosus is the cutaneous form of lupus erythematosus often involving the exterior of the nose. Dull, red macules may be found, which later heal with atrophy, scarring, dyspigmentation, and telangiectasia. The diagnosis of SLE requires meeting certain number of clinical manifestations in addition to a positive findings on autoantibody studies (i.e. ANA, anti-DNA, anti Ro). The American Rheumatism Association has set forth the criteria for diagnosis. Treatment consists of non-steroidal anti-inflammatory drugs, glucocorticosteroids, and anti-malarials, while cytotoxic chemotherapy (azathioprine, chlorambucil, cyclophosphamide) is used for the more severe, resistant cases.

Sjogren’s syndrome afflicts mainly middle aged women (9:1 female to male predilection) and characterized as an immunologic disorder which produces progressive destruction of the exocrine glands. The primary form of the syndrome (sicca complex) only involves the exocrine glands versus the secondary form in which there is a connective tissue disease having the sicca complex as a manifestation. The mechanism of injury is related to lymphocytic infiltration and immune-complex deposition in the tissues. The salivary and lacrimal glands are predominately involved, causing a sicca syndrome, which presents with xerostomia and xerophthalmia with secondary keratoconjunctivitis as the mucosa and conjunctiva become dry as the glandular tissue dysfunctions. Dental caries is also a common complication. Systemic involvement of the disease includes glomerulonephritis (40%), vasculitis (25%), sensory polyneuropathy, Raynoud's phenomenon, thyroid disease resembling Hashimoto's thyroiditis, and interstitial pneumonitis. Interestingly, approximately 10% of the patients develop a pseudolymphoma which presents as lymphadenopathy, splenomegaly, parotid gland enlargement, or pulmonary nodules--10% of this group later develop a non-hodgkin's lymphoma. A triad of keratoconjunctivitis sicca, xerostomia, and histopathology showing mononuclear cell infiltration into the exocrine gland is basis for diagnosis. Minor salivary gland biopsy is typically used, with specificity in the 50 - 95% range. Detection of antibodies directed to the Sjogrens's syndrome antigen is also useful (SS-A and SS-B). Of note, ANA is positive in approximately 50%-70% of the patients. Treatment is generally aimed at relieving the symptoms by lubricating tears, nasal sprays of normal saline, and proper oral hygiene.

Churg-Strauss Syndrome has been described as an allergic angiitis and multi-system granulomatous vasculitis. The mean age of onset is estimated at 44 with a male to female ratio of 1.3:1. Pathologically, the granulomatous lesion occurs in small to medium size arteries, capillaries, veins, and venules with an associated infiltration of eosinophils in the tissue. The pathogenesis of the disease is uncertain, but is most likely related to an aberrant hypersensitivity phenomena. The disease has three phases: (1) a prodromal stage, allergic disease predominates consisting of allergic rhinitis, nasal polyposis, nasal stuffiness, and an element of asthma, (2) hypereosinophilia is striking in the second phase--peripheral blood eosinophilia, chronic eosinophilic pneumonia, or eosinophilic gastroenteritis, and (3) a wide spread vasculitic disease which may have fatal results. Diagnosis is based on biopsy, which shows the allergic granuloma characteristic of this disease.
Treatment consists of high dose glucocorticosteroids, with a 50% 5 year survival if treated properly.

**BIBLIOGRAPHY**


