Pathophysiology

Neutrophils usually remove agents that initiate an acute inflammatory response by phagocytosis and digestion. If an agent is indigestible it provokes a vicious cycle of acute inflammatory responses that can cause local tissue damage. The body deals with these reactions by forming granulomas. Macrophages and lymphocytes are the principle cells involved in granulomatous inflammation. Macrophages live longer than neutrophils and can phagocytose an indigestible agent. This causes macrophages to lose their motility and thus accumulate at the site of injury. They then undergo structural changes and become epithelioid cells which are larger with more cytoplasm and resemble epithelial cells and become surrounded by lymphocytes. When these cells (50+) fuse together they form multinucleated giant cells. When the nuclei of these giant cells form a horse show pattern, the cell is named a “Langhans Giant Cells”.

INFECTIOUS

Bacterial

*Cat Scratch Disease:*

Cat Scratch Disease (CSD) is caused by a gram-negative rod. It is considered to be the most common cause of chronic benign adenopathy in children and young adults. 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. CSD is initially manifested as 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. Preauricular and submandibular lymphadenopathy is most common. Parinaud oculoglandular syndrome involves granulomatous non-suppurative conjunctivitis and adjacent ipsilateral pre-auricular lymphadenopathy. 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. Serology (IgG, IgM) is used for diagnosis. FNA will show pyogenic granulomas early in the disease process and Necrotizing granulomas later in the disease. B. Henselae require special staining for detection. Azithromycin for 5 days has shown to
speed resolution of lymphadenopathy. 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.

**Bacillary angiomatosis:**

(BA) is an uncommon vascular proliferative manifestation of infection with B. henselae that occurs in patients that are immunosuppressed/HIV positive. Manifestations of BA are vasculoproliferative cutaneous 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. Like CSD, BA is diagnosed with serology (IgG, IgM) and with warthin-starry stain. BA requires antibiotic treatment. Erythromycin for 3-4 weeks is the treatment of choice; the duration depends on the extent of bone or visceral involvement. Extensive or fulminant disease may require intravenous erythromycin. An alternative antibiotic is doxycycline.

**M. Tuberculosis:**

This is a 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. In the head and neck cervical adenitis (scrofula) is the most common form of extrapulmonary disease. The lymph nodes are bilateral, multiple, matted and non-tender. Most commonly, involves the posterior triangles of the neck. It can also manifest as single or multiple lesions in the oral cavity. The tongue is most commonly involved also seen in the gingiva, dental sockets and buccal folds. The larynx is involved in approximately 1% of patients who have active pulmonary TB. The true vocal cords are most commonly involved followed by the arytenoids, posterior commissure, and subglottis. Although less common otologic involvement may be found, presenting as serous otorrhea, multiple small perforations and pale granulation tissue with in the middle ear. 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 (Ziehl-Neelsen) and cultures should reveal acid fast bacilli. Extrapulmonary TB can be diagnosed by positive blood culture or biopsy. Biopsy will show necrotizing granulomas with acid fast bacilli. PPD is used for TB screening. 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. Lymphnode excision may lead to chronically draining fistula.
**Atypical Mycobacterium:**

Important pathogenic bacteria in this group are M. avium complex, M. kansasii, M. scrofulaceum and M. marinum. It is most commonly seen in children and immunocompromised patients. Head and neck manifestations include corneal ulcerations, non-tender unilateral cervical lymphadenopathy (scrofula) within the anterior, pre-auricular, submandibular regions. Lymphnodes are discrete separate and may progress into an abscess. Diagnosis is made by excisional biopsy of the involved lymphode with acid fast staining of the bacilli. Treatment includes surgical excision and Erythromycin, Rifampin or streptomycin.

**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. Catarhal 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:**

Mycobacterium Leprea is the organism that causes Leprosy (Hansen’s disease), a chronic granulomatous infection which involves superficial tissues such as the 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. The tuberculoid form is characterized by massive involvement of peripheral nerves resulting in severe pain and muscle atrophy. Cutaneous hypopigmented lesions can also occur but are less common. Peripheral nerve involvement is asymmetric. In lepromatous leprosy, Cutaneous lesions are more common than peripheral nerve involvement. Peripheral nerve involvement is symmetric. The organisms produce nodular skin lesions involving the brows, cheeks, nose and ear commonly referred as Leonine facies. Involvement of the nasal mucosa occurs in 95% of patients. Nasal mucosa appears nodular, pale-yellow and thickened. The anterior nasal septum and anterior inferior turbinates are commonly involved. Nasal involvement can lead to saddle nose deformity, epistaxis, chronic rhinorrhea. M.
Leprea can involve the soft/hard palate and larynx manifesting as ulcerative, nodular lesions. Diagnosis is by nasal/skin scrapping, which on culture staining show the organism or can reveal granulomatous changes. Treatment for tuberculoid is usually dapsone and rifampin, for lepromatous it is usually dapsone, rifampin and clorfazimine.

**Syphilis**

Syphilis is 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, particularity when the gummatous lesion causes an obliterative endarteritis. Due to the reduced blood supply, the bony labyrinth necrosis, 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.

**Actinomycosis:**

Actinomycosis is an indolent suppurative infection caused by an anaerobic or microaerophilic organism. It is a filamentous, branching, gram-positive bacilli. It is found as normal flora of the oral cavity. 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.

**Rhinoscleroma**

Rhinoscleroma is caused by Klebsiella rhinoscleromatis, which has three distinct phases: (1) catarrhal stage (atrophic)—prolonged purulent rhinorrhea honeycombed nasal crusting, in the larynx it presents with hoarseness, interarytenoid hyperemia and vocal fold edema (2) granulomatous stage is 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 surgical debridement and streptomycin or tetracycline. Patients with significant stenosis may require dilatation procedures.

**Fungal Infections**

**Histoplasmosis:**

*Histoplasma 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. It is found in soil enriched with bird, chicken or bat excrement. 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. Head and neck 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. H&E stains will show non-caseating granulomatous inflammation. Urine and serum samples can be
tested for H. capsulatum antigen. Amphotericin B continues to be the treatment of choice, but newer less toxic antifungal agents are currently being tested.

**Blastomycosis**

*Blastomyces dermatitidis* is a dimorphic fungus found in moist soil 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 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. The larynx and hypopharynx may be involved, showing areas of erythematous hyperplasia and ulceration on examination. Lesions are easily mistaken for SCCA. True vocal cords are the most commonly involved laryngeal site. 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. Gomori staining will show broad-based budding. Treatment is amphotericin B.

**Coccidioidomycosis:**

*Coccidioides immitis* may cause a granulomatous type inflammatory reaction. It is endemic to southwestern US, found in soil of dry climates and is known as “Valley Fever”. Common head and neck manifestations include submucosal nodules and edema of the larynx, cervical lymphadenopathy, and erythema nodosum/multiforme. Biopsy will show a granuloma with spherule with endospores. Serology is very specific and sensitive. Treatment includes Itraconazole and Amphotericin B.

**Rhinosporidiosis:**

*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 and cauterization at the base.

**Aspergillus:**

*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 (fungus ball) of the disease usually involves a single sinus cavity usually the maxillary and sphenoid sinus. Symptoms include thick, dark nasal secretions, and fullness as presenting complaints. Allergic fungal sinusitis occurs when an antigen for an allergic response results in allergic mucin and nasal polyps. Multiple sinuses are typically involved. In the invasive form (soft tissue and bone) of the disease, patients may present with
facial hypesthesia, proptosis, ophthalmoplegia, and possible visual loss. The invasive form affects immunocompromised patients with history of diabetes, diabetic ketoacidosis, HIV and patients undergoing chemotherapy. Mucormycosis is more invasive and can cause vascular occlusion, thrombosis, and necrosis. Clinical finding in Mucor are black turbinate sans septum. 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.

Autoimmune/Vasculitis

Sarcoidosis:

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 10-80 per 100,000, most common amongst African americans. It generally occurs during the second to fourth 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 (bilateral hilar lymphadenopathy), 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. Heerfordt’s syndrome (Uveoparotid fever) presents as a chronic febrile course, bilateral parotid gland swelling, uveitis and facial nerve palsy. In 5% of the cases, the larynx and the supraglottis, may demonstrate an erythematous, edematous, nodular, and non-ulcerated mucosa, with airway obstruction as a symptom. The epiglottis is most commonly affected and appears as a turban like thickening. Diagnosis of sarcoidosis requires a combination of radiographic, clinical, and histologic positive findings (non-caseating granuloma). 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 (Methotrexate) or antimalarial drugs (Hydroxychloroquine and chloroquine) are used for treatment.

**Wegener's Granulomatosis:**

Wegener's Granulomatosis recently known as Granulomatosis with polyangiitis is a systemic disease, thought to be autoimmune, characterized by vasculitis and predominantly epithelioid necrotizing granulomas in the involved tissue. It’s prevalence is 3 in 100,000; men and women are equally affected. 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) and saddle nose deformity. Otologic involvement occurs in 20-25% of the cases with serous otitis media and possible sensorineural hearing loss related to cochlear vasculitis, it can also cause swelling and tenderness of the external ear. 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. Initial goal of treatment is to induce remission (Cyclophosphamide or Methotrexate or Azathioprine plus high dose steroids). Maintenance therapy includes Trimetoprim-sulfamethoxazole. Rituximab, Etanercept and Lefunomide are investigational therapies.

**Rheumatoid arthritis:**

Rheumatoid arthritis (RA) is an autoimmune disease causing inflammation of synovial joints. It is more common in women than men (3:1). Head and neck manifestations include TMJ dysfunction, cricoarytenoid joint involvement with ankylosis and submucosal nodules of vocal cords. It can also cause CHL secondary to ossicular joint involvement. RA can be diagnosed clinically with morning stiffness, symmetric polyarthritis and subcutaneous nodules. Elevated RF, ESR and chest xray will show nodules, pleural effusion and fibrosis. Biopsy will show necrotizing granulomas. Treatment includes NSAIDS, ASA, prednisone and methotrexate.

**Systemic lupus erythematosus:**

Systemic lupus erythematosus is a disease in which tissues are damaged by deposition of autoantibodies and immune complexes. There is a definite gender predilection affecting females more commonly than med (9:1). 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). Treatment consists of non-steroidal anti-inflammatory drugs, prednisone, and methotrexate.

Relapsing Polychondritis:

This is a rare inflammatory disease of cartilaginous structures (ears, nose, joints and tracheobronchial tree). Patients produce antibodies to type II and type IV collagen. 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. SNHL, tinnitus and vertigo can result secondary to vasculitis of labyrinthine artery. 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. Treatment includes high dose prednisone, Dapsone, NSAIDs, Methotrexate and Cyclophosphamide.

Churg-Strauss Syndrome:

Churg-Strauss Syndrome has been described as a multi-system granulomatous vasculitis. The mean age of onset is estimated at 50 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 disease has three phases: (1) a prodromal stage, allergic disease predominates consisting of allergic rhinitis, nasal polyposis, nasal stuffiness, and adult onset 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 necrotizing granuloma characteristic of this disease, p-ANCA is found in 70% of patients, leukocytosis with >10% eosinophils and elevated IgE. Treatment consists of high dose glucocorticosteroids, with a 50% 5 year survival if treated properly.

Neoplastic

Langerhans Cell histiocytosis

Langerhans cell histiocytosis (LHC) is a granulomatous disease of unknown etiology and commonly affects children. Histology will show proliferation of Langerhans cells, eosinophils, macrophages and lymphocytes. Electron microscopy will show Birbeck granules in cytoplasm of
langerhan cells. Immunohistochemistry staining will stain positive for S-100. LCH was previously divided into the following subsets:

1. 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 ages 5-9. This disease process is considered the localized form of histiocytosis X. It has a benign course with a good prognosis. Treatment is surgical excision with low dose radiation therapy used for recurrent lesions.

2. Hand-Schuller-Christian disease is considered to be a chronic, multifocal form of histiocytosis X. This tends to be a disease of children less than 5 years old. 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 consists of low dose radiation therapy. Despite treatment, the mortality rate approximates 30%.

3. Letterer-Siwe is considered to be disseminated disease of infants (<2 years old) 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. It has a poor prognosis and high mortality rate. Treatment consists of chemotherapeutic agents, but the disease is uniformly fatal in 1-2 years.

**Necrotizing sialometaplasia:**

Necrotizing sialometaplasia is a benign self healing inflammatory process of minor salivary glands. It 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. The lesion resolves spontaneously within two to three months, and does not need excision unless the mass effect is interfering with deglutition or dentures.

**NK/T-Cell lymphoma:**

Polymorphic reticulosis, lethal midline granuloma, and lymphomatoid granulomatosis, angiocentric lymphoma, are synonymous terms used previously to describe a condition that is now known as Nasal NK/T-Cell lymphoma. 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. 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. 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 plus chemotherapy.

References