1. (DJ) Tell us about the different types of Histiocytosis X and the head and neck manifestations of it.

**Histiocytosis X (Langerhans Cell Histiocytosis)**
- Proliferation of cells that arise from BM & found circulating w/ blood & LNs at junctional areas b/w body & outside environment (epithelial & endothelial surfaces). Normal role of histiocyte is to present Ag to T & B cells.
- Typically dz of children, although it can occur at any age
- 3 standard presentations:
  - Localized (Group 1 - often children b/w 5 & 9): monostotic bone dz [formerly called Eosinophilic granuloma]
  - Multifocal (Group 2 - children b/w 2 & 5): polyostotic bone dz; with two or more osseous, cutaneous, or soft tissue lesions with or without endocrine abnormalities [formerly called Hand-Schuller-Christian]
  - Disseminated (Group 3 - <2 yrs of age): found throughout body & a/w vital organ dysfunction [formerly called Letterer-Siwe]
- Pathogenesis – unclear; most likely represents an immune dysfunction. May represent a low-grade type of lymphoma. Langerhans cells→ mononuclear cells under microscope; see characteristic Birbeck granule or X-body w/ electron microscope (“tennis racket”)
- Clinical Findings
  - Most common presenting symptoms: swelling of the skull (45%), cervical adenopathy (25%), cephalic rash (20%), & otorrhea (20%).
  - Within the temporal bone, the disease often masquerades as otitis media, mastoiditis, & otorrhea that fail to resolve with antibiotic therapy.
  - Conductive hearing loss is often noted, & an aural polyp may be realized during the physical exam.
  - Langerhans cell histiocytosis should be considered in all children with aural polyps & chronic otitis media.
  - Facial nerve paralysis, vertigo, dysequilibrium, tinnitus, & sensorineural hearing loss are rare.
  - Disseminated dz presents w/ failure to thrive, fever, & extensive systemic involvement.
- Imaging Studies
  - Plain radiographs of the skull often reveal multiple lytic skull lesions.
  - CT reveals soft tissue mass with diffuse irregular bone destruction.
  - MR - intermediate intensity lesions on T1 & high intensity on T2
- Treatment
  - Surgical- diagnostic biopsy & curettage; usu all that is required for localized & most cases of multifocal dz
  - Nonsurgical- chemo/radiation commonly used for disseminated dz


**Sarcoidosis** is a systemic disease and pulmonary findings are present in 90% of cases. Head and neck manifestations are found in 10 to 15%. ENT manifestations include:
1. Posterior cervical chain lymphadenopathy (usually discrete nodal involvement that is symmetric and nontender)
2. Skin lesions (including Lupus pernio, Hutchinson's plaque and papular sarcoid)
3. Nasal involvement (13%) usually presents as obstructive symptoms with discharge. Mucosal lesions, when present in the nose, appear as firm submucosal, yellow nodules and are almost diagnostic of sarcoidosis. The article referenced in question is “Diagnostic criteria for sarcoidosis of the sinuses”
4. Parotid gland involvement is common and is usually bilateral and nontender.
5. Facial nerve palsy are the most common cranial nerve deficit but any cranial nerve can be affected. Paresis can be fluctuating or progressive.
6. Laryngeal sarcoid (1 - 5%) is commonly found in patients with no pulmonary manifestations. The supraglottic area is most commonly affected but the subglottic region can also be involved. True vocal cords are rarely affected. Localized, pale edema, punctuate submucosal nodules, and mass lesions have been described. Pale edema is the most common presentation.

Diagnosis requires **tissue evaluation** to rule out other granulomatous diseases and biopsies should be analyzed with fungal and mycobacterial cultures and stains. Noncaseating granulomas are the hallmark of the disease. Common areas biopsied include superficial lymph nodes, salivary gland tissue and tail of the parotid. **Serologic testing** can support the diagnosis of sarcoidosis, but no single test is diagnostic. Tests include Erythrocyte Sedimentation Rate (ESR) and the Angiotensin Converting Enzyme level (ACE). ACE levels are elevated in 60% of patients with sarcoidosis. Another useful test is the **gallium-67 scan**. It is a more sensitive measure of pulmonary involvement than plain chest X-rays and can also detect subclinical disease in the parotid gland. The combination of elevated ACE and a positive gallium-67 scan is 85% specific for sarcoid.

Many patients will show spontaneous resolution without treatment. When pulmonary or laryngeal manifestations are present, treatment is generally required. Extrapulmonary manifestations require treatment when major organs, neurologic, ocular, deforming skin lesions, or aerodigestive tract involvement are present. **Oral steroids** remain the cornerstone of treatment, but there is no set
protocol. Patients are usually treated for at least six months initially. ACE or the ESR levels can be used to monitor response. Local steroids (topical or nasal sprays) can be used to treat skin or nasal involvement. Some authors have advocated intralesional steroids for supraglottic laryngeal involvement, but this requires a general anesthetic with each treatment. There have been 5 reported cases of glottic sarcoidosis treated with external beam radiation therapy. 4/5 patients failed therapy and one patient later developed laryngeal carcinoma.

3. (Amy) Contrast and compare head and neck manifestations and treatment of tuberculosis vs. nontuberculous mycobacterial infections.

Nontuberculous mycobacteria are less virulent, more likely to infect individuals who have altered host defenses, and less susceptible to standard antituberculosis drugs. *Mycobacterium scrofulaceum*, *Mycobacterium szulgai*, and *Mycobacterium xenopi* are common pathogens. Other manifestations include infected cervical lymph nodes and corneal ulcers from inoculation of the eye with contaminated dust. Atypical mycobacterial infections typically occur in pediatric populations and present as a unilateral neck mass in the anterior triangle or parotid with painful and indurated skin. Diagnosis is by culture and skin testing. Surgical excision is the definitive treatment, although incision and curettage with antibiotic therapy is an alternative.

Tuberculous infections are caused by *Mycobacterium tuberculosis* and, rarely, *Mycobacterium bovis*. They tend to be associated with diffuse and bilateral lymphadenopathy and are usually responsive to antituberculous medications. Tuberculin skin tests are strongly positive. Nasal tuberculosis usually affects the anterior septum or anterior portion of the turbinates with sparing of the nasal floor. The symptoms begin with nasal discharge, pain, and partial obstruction with red, nodular thickening on exam. The disease can progress rapidly and result in scarring or perforations of the cartilaginous portion of the septum. Cervical tuberculosis (scrofula) tends to occur in immunocompromised patients. Surgery is effective in establishing the diagnosis, but surgical excision alone has a high rate of recurrence and fistula formation. The standard treatment is medical.

4. (Kathy) Tell us about midline lethal granuloma and the-cocaine induced midline granulomas?

Lethal midline granuloma (LMG), also known as nasal natural killer T-cell lymphoma (NTL) is a rare entity that results in a destructive process of the facial midline, and may appear as a symptom of various infectious, malignant or autoimmune diseases. It exhibits a male preponderance, and has a wide age range. This EB virus-associated aggressive lymphoma, which is more prevalent in Asia, commonly presents with midline facial destructive lesions and are usually responsive to antituberculous medications. It is believed to be through the mouth, and the tonsils have been implicated in particular. Infection by *Mycobacterium avium-intra-cellulare*. These organisms are commonly found in soil, water, domestic and wild animals, mild and other food items. The portal of entry is believed to be through the mouth, and the tonsils have been implicated in particular. Infection by *M. bovis* has decreased dramatically with the institution of milk pasteurization. Typical presentation is of a rapidly enlarging and persistent unilateral anterior neck mass that has failed to respond to antibiotics in a pediatric patient. The skin becomes adherent to surrounding tissues and develops a characteristic violaceous discoloration. Treatment is clarithromycin and/or surgical excision.

Case reports of heavy intranasal cocaine use have resulted in a destructive process of the facial midline similar to presentation of LMG-NTL, with necrosis and atrophy of turbinates, septum, and palate. However, on biopsy, there is no evidence of focal vasculitis or granuloma formation, just chronic inflammation and necrosis.

5. (Kathy) What are the granulomatous diseases that you can pick up from living with animals (farm and otherwise).

Nontuberculous mycobacteria (NTM) causes majority of cervicofacial infections in young children, most cases occurring in those under 5 years of age. The specific organisms most commonly classified as NTM are *M. kansasii*, *M. scrofulaceum*, and *M. avium-intra-cellulare*. These organisms are commonly found in soil, water, domestic and wild animals, mild and other food items. The portal of entry is believed to be through the mouth, and the tonsils have been implicated in particular. Infection by *M. bovis* has decreased dramatically with the institution of milk pasteurization. Typical presentation is of a rapidly enlarging and persistent unilateral anterior neck mass that has failed to respond to antibiotics in a pediatric patient. The skin becomes adherent to surrounding tissues and develops a characteristic violaceous discoloration. Treatment is clarithromycin and/or surgical excision.

Cat scratch disease (CSD) is a granulomatous lymphadenitis that most commonly results from cutaneous inoculation caused by scratch trauma from the domestic cat. The causative organism is classified as *Bartonella henselae*, a gram-negative bacilli. Approximately 90% of patients who have CSD report a history of exposure to cats, and 75% of these patients have experience a cat scratch or bite. The major vector by which cats themselves are believed to become infected is the cat flea. The typical history is of a papule or pustule at the scratch or bite site followed in 1 to 2 weeks by the development of LAD in the region of inoculation. The nodes will slowly enlarge over a period of 1 to 2 weeks and might not resolve for 2 to 3 months. Erythema, fluctuance, spontaneous suppuration, fever and mild systemic symptoms may occur in up to one-third of patients. Antibiotics reported to be most effective are rifampin, erythromycin, azithromycin, gentamicin, and ciprofloxacin.

6. (Josh) Osler once said, "If you know syphilis, you know medicine." Tell us what you know about the stages of syphilis and head and neck manifestations.
Osler once said, "If you know syphilis, you know medicine." Tell us what you know about the stages of syphilis and head and neck manifestations.

**Pathophysiology:** chronic infection caused by spirochete Treponema pallidum, usually sexually transmitted or from maternal transmission

**Stages:**
- **PRIMARY:** initial stage, chancre at inoculation site (penis, cervix, anal canal, **oral**), appears 3 weeks after exposure heals in a few weeks, *lymphadenopathy*
- **SECONDARY:** “The great imitator,” highly contagious, general malaise, fever, arthralgia, hepatosplenomegaly, genital condyoma lata, nephrotic syndrome, “mucous patches” on any cutaneous or mucosal surface—grayish superficial mucous membrane patches surrounded by erythematous border, diffuse laryngeal hyperemia accompanied by diffuse coalescing maculopapular rash in supraglottic region, may progress to condritis, fibrosis, **searing**
- **LATE**
  - **LATENT:** asymptomatic, may have return to **mucocutaneous lesions**
  - **TERTIARY:** rare, may occur years after initial infection, slowly progressive, **characterized by gummata (rubbery textured granulomatous disease with necrotic center in any body tissue), affects CNS (neurosyphilis), and cardiovascular (aorta)**
  - **REMISSION:** 1/3 resolution
- **H&N symptoms:** usually 2/3 osseous and cartilagenous destruction, granulomatous dz, gummata, or obliterative arteritis
  - generalized cervical adenopathy, laryngitis and vocal fold paralysis (rare), oral chancres, granulomatous infiltration of tongue and palate, SNHL (80% in symptomatic neurosyphilis, 29% in asymptomatic neurosyphilis, 25% in latent), abrupt profound unilateral or bilateral SSNHL (incidence of syphilis at any stage <2%), Meniere’s symptoms, interstitial keratitis, TM perforation, saddle nose deformity, rhinitis, septal perforation, endolymphatic hydrops causing resorptive osteitis and fibrous adhesions between the stapes footplate and membranous labyrinth, Hennebert’s sign (positive fistula test or ocular deviation with positive or negative pressure in absence of middle ear disease) Tullio’s phenomenon (vertigo or nystagmus on exposure to high-intensity sound)

**Congenital syphilis:** often fatal, Hutchinson’s Triad (abnormal incisors or Hutchinson’s teeth, interstitial keratitis, deafness), cutaneous lesions, hepatosplenomegaly, lymphadenopathy, larynghitis, Clutton’s joints (bilateral knee effusions), neurosyphilis, “mulberry molars,” frontal bossing, mental retardation, saddle nose deformity (from epiphysitis), SNHL in 17%

**Dx:** non-specific screening RPR or VDRL, specific FTA-ABS, dark field microscopy, Warthin-starry tissue staining

**Histopathology:** mononuclear infiltrate, obliterative arteritis, hydrops, gummata and osteolytic lesions in otic capsule

**Rx:** penicillin, ampicillin, tetracycline, erythromycin, corticosteroids for otologic involvement, treat until serologic markers normalize

7. (DR) Discuss fungal granulomatous diseases of the head and neck.

**Actinomycosis** – Most often presents as slowly growing, painless, firm, possibly suppurating submandibular mass, but it can also present as a rapidly progressive, painful, fluctuant infection anywhere in the neck or face. It is typically associated with fever and leukocytosis. Pus characteristically contains sulfur granules. Usually seen in people with poor oral hygiene and oral mucosal trauma, sometimes follows dental manipulation or trauma. Treated with long-term, high-dose penicillin.

**Aspergillosis** – May present as invasive sinus infection in immunosuppressed patients. Persistent pain and discharge are common symptoms. 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. Treatment consists of rigid nasal endoscopy and aspiration of sinus contents, followed by long-term amphotericin B therapy.

**Blastomycosis** - Found throughout U.S. Skin and larynx are most common extrapulmonary sites of involvement. Can mimic SCCA or verrucous carcinoma. Usually found in diabetics or otherwise immunocompromised patients. Treated with amphotericin B, or with several months of oral ketoconazole/itraconazole.

**Candidiasis** – Infection is typically endogenous and results from host immunosuppression. Other than oropharyngeal thrush, may present as surface irregularities of esophageal mucosa, sometimes with cobblestoning or nodules. Also can cause angular cheilitis. Treatment is with oral antifungals.

**Cryptococcosis** - Found in bird droppings and surrounding soil. In immunocompromised patients, especially with AIDS, may present with cutaneous involvement of head and neck (mimics molluscum contagiosum or Kaposi’s sarcoma). Treatment with oral and IV antifungals.

**Histoplasmosis** - Endemic to Ohio and Mississippi River valleys (80-90% of population infected). May present as mucosal ulcers of upper aerodigestive tract - flat, plaquelike nontender elevations or nodules that later ulcerate and become painful. Can also present with fibrosing mediastinitis or mediastinal granulomas (common cause of SVC syndrome). Treated with amphotericin B.
Rhinosporidiosis - Primarily found in southern India and Sri Lanka. Spread by contaminated water. May be found as strawberry lesions - painless, warty lesions on mucous membranes of head and neck, particularly nasal mucosa. Treatment consists of excision and oral antifungals.

Sporotrichosis – Usually seen as raised, painless, erythematous nodules of facial skin, but cases of sinusitis, orbital osteomyelitis, nasal obstruction, and stridor from laryngeal involvement have been reported.

8. (DR) What are the specific locations in the larynx where the different granulomatous dz's manifest.

Relapsing polychondritis - May affect epiglottis or subglottis

SLE - Glottis and cricoarytenoid joints most commonly affected; supraglottic and subglottic involvement have been reported.

Sarcoidosis - Typically presents as submucosal mass in supraglottis, most commonly a a pale, edematous mass in the epiglottis. Also seen in AE folds and false cords. True vocal cord involvement is rare, possibly due to lack of lymphatics.

Rhinoscleroma - Manifests in glottis and subglottis during second stage (florid or granulomatous stage)

Wegener’s - Up to 23% of patients have laryngeal involvement. Almost exclusively confined to subglottis.

Amyloidosis – Rarely involves larynx. Accounts for as little as 0.2% of benign laryngeal tumors. Most commonly affects true vocal cords, ventricle, and false cords.

Tuberculosis - Formerly the most common disease affecting the larynx. Almost any area of the larynx can be involved, especially supraglottic structures such as the AE folds and epiglottis. Lesions range from areas of nonspecific inflammation to a nodular, exophytic lesion or mucosal ulcerations.

Syphilis - Laryngeal involvement is rare. Secondary syphilis may present as diffuse laryngeal hyperemia, accompanied by coalescing rash of supraglottic region. Tertiary syphilis appears as a diffuse, nodular, gummatous infiltrate.

Hansen's disease (leprosy) - Larynx is second most frequent site of involvement in head and neck (after nose). Usually presents initially as erythematous or nodular edema of the supraglottis and progresses secondarily to glottis.

Fungal infections -
- Histoplasma - Any part of larynx
- Blastomyces - True cords most commonly by far, sometimes with extension to false cords
- Cryptococcus - True cords are usually only site affected
- Actinomycetes - Any part of larynx

9. (CY) Why are intubation granuloma, reparative granuloma, and pyogenic granuloma not granulomatous diseases? Tell us about each and their treatment.

None of these demonstrate the characteristic histologic features of a granuloma. The histologic definition of a granuloma, an inflammatory infiltration is composed of compact aggregates of epithelioid macrophages. Most present as granulomas with peripheral lymphocytes, central epithelioid histiocytes and, usually, multinucleated giant cells

1. Intubation Granuloma- Almost invariably involves the vocal process of the arytenoid
Occurs only in adults F>>M
Progression: contact ulcer=> granuloma=> pedunculated polyp
Treatment: observation, antibiotic use, voice therapy in select group, corticosteroid injection, surgical excision

2. Reparative Granuloma- Etiology unknown, but felt to be secondary to local trauma.
Types- 1. peripheral: sessile or pedunculated mucosa-covered reddish or bluish mass arising from the gingiva or alveolar mucosa, most common on the anterior mandible. 2. central: endosteal lesion, usually anterior to the first molar in the mandible, radiographically will appear as a lytic, expansile, unilocular cavity with well-demarcated, non-sclerotic margins; the bony cortex will be thinned but intact. Treatment-curettage.

3. "Pyogenic Granuloma" - neither infectious or granulomatous, also called lobular capillary hemangioma, common benign vascular lesion of the skin and mucosa
- cause unknown – poss secondary to minor trauma with secondary infection
- usually in children and young adults as a solitary glistening red papule or nodule that is prone to bleeding and ulceration. It typically evolves rapidly over a period of a few weeks
Oct 4: Granulomatous Diseases of the H&N (updated 09/06)

Treatment
- Medical: Topical imiquimod cream and alitretinoin gel, intralesional and systemic steroids, especially for PG with satellitosis
- Surgical Care: Shave, punch, scalpel, or laser excision may be curative. Sclerotherapy, chemical cauterization with silver nitrate, ligation of the base, and cryotherapy have all been reported effective.

Wegener’s Granulomatosis is a vasculitis of small to medium sized vessels that can affect multiple organ systems. Symptoms are non-specific, and the disease is often only suspected after a patient has had unexplained symptoms for a long period of time. Patients frequently present with a URI unresponsive to antibiotics and associated with serosanguinous nasal drainage and pain. The pain is most severe over the dorsum of the nose, and large nasal crusts are present in both sides of the nose. Patients may also have crusting in the nasopharynx overlying friable mucosa. No other disease has such severe crusting.

Nose: pain, congestion, rhinitis, epistaxis, crusting, perforated septum, saddle nose deformity
Ears: CHL (eustachian tube dysfunction), SNHL (unclear mechanism), unilateral or bilateral SOM +/- mastoiditis
OC/OP: rare, diffuse upper/lower gingival lesions, diffuse minor salivary gland involvement with oral ulcerations
Sinus: sinonasal bone destruction, nasolacrimal obstruction due to ethmoid and nasal disease
Trachea: subglottic stenosis
Eye: pseudotumor or extension into the orbit resulting in unilateral or bilateral proptosis, scleritis, conjunctivitis, uveitis, episcleritis

Determination of a c-ANCA level can aid in the diagnosis, but a positive result is not conclusive and a negative result is not sufficient to reject the diagnosis. Histopathology reveals vasculitic necrosis with an inflammatory background; intramural necrotizing granulomatous lesions are surrounded by palisading histiocytes and scattered giant cells. Initial treatment is generally with corticosteroids (1 mg/kg/day) and oral cyclophosphamide (2 mg/kg/day). Treatment with cyclophosphamide is continued for at least 6 months to 1 year and tapered after the disappearance of symptoms. Bactrim is often used in conjunction with the above treatments and as prophylaxis after patients have completed immunosuppressive therapy. In the case of severe subglottic stenosis, tracheotomy may be required to maintain an airway.


Sarcoid involves H&N in 9% of sarcoid cases, 1% in sinonasal cavity.
Present with chronic nasal congestion, recurrent infections, anosmia. Exam reveals pale yellow submucosal nodules at anterior septum and inf. Turb.
Noncaseating granulomas are hallmark of disease.
Case series of 6 patients after FESS for recurrent nasal symptoms, only four with biopsy confirmed disease.
Treatment: Steroids, nasal irrigation. Abx if exacerbation of symptoms or rhinosinusitis. And FESS to enhance mucociliary clearance.


This information comes from the article entitled “The role of endoscopic sinus surgery in chronic sinonasal sarcoidosis" by David J. Kay and Gady Har-El, American Journal of Rhinology 2001. As the article points out, sarcoidosis most often affects the lungs but can involve the sinonasal system in up to 1% of patients and usually presents as nasal obstruction. It may be the first complaint and often involves the septum and inferior turbinates. Corticosteroids are typically used in treatment of sinonasal disease. Topical nasal sprays as well as local injections have been traditionally used. Surgery has been reserved for biopsy or complication of sinonasal disease. This article is the first to advocate the use of ESS as primary treatment in sinonasal disease for those patients with significant blockage. Patient selection is extremely important and patients from this study were those without active pulmonary disease who were not on systemic steroids. Only 7% of patients who presented with sinonasal disease were operated on. The surgery provided an opening to which topical nasal steroids could be applied.