

## Chapter 59: Infections

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Infections of the salivary glands may take various forms depending on the etiologic agents involved and the chronicity of the infection. Bacterial infections of the salivary gland are typically the result of mechanical blockage of the salivary ducts or reduced production of saliva, which permits retrograde bacterial contamination of the gland parenchyma. Certain systemic viral infections, such as mumps and acquired immunodeficiency syndrome (AIDS), produce localized salivary gland disease. Many granulomatous infections, through their involvement of the lymphoreticular system in and around the gland parenchyma, can produce pathologic changes in the salivary glands.

### Primary Infections of the Salivary Glands

#### Acute suppurative sialadenitis

Historically, because of its frequent postoperative occurrence and the common involvement of the parotid gland, some of the terms associated with acute suppurative parotitis have included *surgical parotitis*, *surgical "mumps"*, *postoperative parotitis*, and *secondary parotitis* (Branson et al, 1959). In acute suppurative sialadenitis the initial infection of salivary gland parenchyma is caused by retrograde bacterial migration from the oral cavity (Berndt et al, 1931). These infections occur in all the major salivary glands, but the parotid gland is most frequently involved, possibly because of the inferior bacteriostatic activity of parotid secretions (Spratt, 1961). Normally, salivary flow constantly flushes contaminants from the ductal system. Stasis of salivary flow permits retrograde migration of bacteria and contamination of the gland parenchyma. Besides stasis of salivary secretions, factors that contribute to the pathogenesis of infection include compromised host resistance and poor oral hygiene (Fig. 59-1).

Most affected patients are in the sixth or seventh decade of life, and the incidence is equal in men and women. Susceptible patients are frequently debilitated due to chronic illness or prolonged recovery from a surgical procedure. Reduction of salivary flow is most frequently the result of dehydration accompanying uncompensated losses of blood and other body fluids following significant hemorrhage, diarrhea, or diaphoresis. Medications with anticholinergic or diuretic side effects further contribute to reduced salivary secretion. Prolonged anorexia reduces the periodic stimulus to salivation and mechanical cleansing associated with mastication. This and the patient's inability to maintain an oral hygiene routine by brushing and flossing result in an increase in the bacterial counts within the oral cavity. Multiple gland involvement is possible, and bilateral involvement occurs in up to 25% of cases of postsurgical parotitis (Lary, 1963; Work and Hecht, 1980).

Local symptoms include a rapid onset of pain, swelling, and induration of the involved gland (Fig. 59-2). Systemic manifestations include fever, chills, malaise, and leukocytosis with neutrophilia. Bimanual palpation of the gland will frequently result in a suppurative discharge from the duct orifice that should be collected for culture and sensitivity studies before the initiation of empirical antibiotic therapy (Fig. 59-3). The most commonly cultured organism among elderly debilitated patients is penicillin-resistant *Staphylococcus aureus*, but

Streptococcus species including *S. pyogenes*, *S. viridans*, *S. pneumococcus*, and *Hemophilus influenzae* are often isolated in community-acquired cases (Lundgren et al, 1976; Mandel, 1976).

Aggressive nonsurgical treatment of the infection includes appropriate parenteral antibiotic therapy using a beta-lactamase-resistant penicillin or cephalosporin, prompt fluid and electrolyte replacement, oral hygiene, and sialogogues. Steroids have also been used to suppress the inflammatory process and potentiate the drainage of material via the salivary duct. Analgesics and local heat application ease the discomfort. Capable patients should be instructed on regular external or bimanual massage, starting from the distal bed of the gland and working in the direction of duct drainage.

Because of parenchymal inflammation and fibrosis, secretory activity of the gland can be permanently reduced. Rarely, conservative measures fail to eradicate the infection and surgical drainage of a loculated abscess is necessary (Fig. 59-4). Suppuration confined to the duct lumen may eventually erode through the epithelium into the interstices of the parenchyma, creating multiple small abscesses that may coalesce into larger collections that may infiltrate a number of potential spaces of the neck (Fig. 59-5). Because of the resistance of the fibrous capsule, particularly that surrounding the parotid gland, palpation of the abscessed gland may fail to reveal fluctuance. Computed tomography (CT) or sonographic imaging of the gland in patients refractory to 3 to 4 days of conservative management may reveal abscess formation. Sialography performed in the acute phases of sialadenitis provides little useful information and is contraindicated because it can exacerbate the existing inflammation. Based on the poor general condition of patients typically at greatest risk, acute suppurative parotitis has been a predictor of poor prognosis in the postoperative patient, associated with mortality in approximately 20% of patients in one study (Lary, 1963).

An algorithmic scheme is helpful in the evaluation and management of localized salivary gland inflammation (Fig. 59-6). The goal of treatment is the sterilization of the glandular secretion and the restoration of normal salivary flow.

### **Recurrent suppurative parotitis of childhood**

A separately recognized recurrent suppurative process of the parotid gland infrequently occurs in otherwise healthy children (Konno and Ito, 1979). Findings include recurrent episodes of glandular swelling, generalized malaise, and pain, frequently following a meal. *Streptococcus viridans* is usually cultured from the ductal exudate. Males are more frequently affected than females, and a history of mumps parotitis often exists.

With appropriate antimicrobial treatment, resolution of swelling and discomfort is generally rapid. Biopsy specimens from involved glands show the persistence of chronic infection between symptomatic phases, which promotes ductal ectasia and abnormally elevates the viscosity of secretions. Sialochemistry shows an increased protein content of the secretions, and sialography demonstrates the characteristic pattern of sialectasis. The damage can be severe enough to predispose the gland to chronic sialadenitis persisting into adulthood, in which case surgical removal of the gland is required. Fortunately most symptoms abate with adolescence and therefore surgical treatment is rarely required (Mandel, 1976).

## **Chronic sialadenitis**

Chronic sialadenitis is a localized condition of the salivary gland characterized by repeated episodes of pain and inflammation, usually culminating in parenchymal degeneration and fibrous replacement of the gland substance. Affected patients frequently experience an initial severe episode of acute sialadenitis. Predisposition to repeated episodes of secondary infection may be attributable to duct obstruction or to ductal dilatation and depressed glandular secretion. Asymptomatic intervals can range from a few weeks to several months. As with acute sialadenitis, the parotid gland is most commonly affected. As the number of inflammatory episodes accumulate, irreversible alteration to the ductal architecture results in diffuse ductal ectasia with intervening areas of stenosis (Fig. 59-7). Periductal and parenchymal inflammatory infiltration and fibrous replacement progress in proportion to the duration of the disease.

Obstruction of salivary flow is a prominent feature of chronic sialadenitis. Mechanical impairment to salivary flow is usually caused by an intraductal calculus, stricture, or mucous plug, but lesions of the ductal papilla and extrinsic ductal compression are occasionally responsible. Typically, the disease is characterized by recurring painful episodes of swelling accompanied by thickening and diminution of saliva.

## **Sialolithiasis**

Sialolithiasis refers to the formation of hardened intraluminal deposits in the ductal system of the salivary glands. Salivary calculi are most commonly discovered in association with chronic sialadenitis, and their development is largely responsible for the recurrent nature of that disease. Approximately 75% of affected patients are in their fifth to eighth decade, yet sialolith development in children and infants has been described (Gorlin and Goldman, 1970). The exact cause of sialolith formation remains unclear, but factors contributing to the development of sialoliths appear to include (1) stagnation of saliva, (2) a focus for sialolith formation resulting from ductal epithelial inflammation and injury, and (3) poorly understood biologic factors favoring precipitation of calcium salts, particularly those associated with chronic inflammation. Formation of sialoliths at the hilus of the gland is most common, although stones may be distributed throughout the ductal system.

Eighty percent of all salivary duct stones develop in the submandibular (Warthin's) duct, with 19% and 1% occurring in the parotid and sublingual duct respectively (Blatt, 1964). A predisposition to formation in the submandibular gland may be related to the composition of the secretions, which are more alkaline and viscous; the submandibular gland contains a higher concentration of calcium and phosphate ions than do other major salivary glands (Mason and Chisholm, 1975). Stagnation of secretions in Warthin's duct may result from the angulation of the duct as it courses around the mylohyoid muscle and the vertical orientation of the distal duct segment.

Compositional differences between the inner and outer lamellae comprising submandibular and parotid sialoliths suggest a different pattern of evolution at these two anatomic sites (Batsakis, 1979). The development of a submandibular sialolith is the primary process that results in impaired salivary flow and ductal inflammation, which secondarily encourages retrograde bacterial migration and resultant sialadenitis. Conversely, parotid

sialoliths may arise because of chronic inflammation that provokes the necessary conditions for calcium formation.

Salivary calculi are most frequently composed of calcium phosphate and carbonate, combined with other salts (Mg, Zn, NH<sub>3</sub>) and organic material (glycoproteins, mucopolysaccharides, and cellular debris), yet there does not appear to be a relationship between their formation and serum calcium or phosphorus levels (Mason and Chisholm, 1975).

Symptoms of sialolithiasis consist of colicky postprandial pain and swelling, with a variable degree of resolution between attacks. Repeated secondary infection causes ductal strictures and parenchymal atrophy. Erosive luminal trauma can result in extrusion of the stone into the gland parenchyma and fistula formation. Diagnosis is made by history and palpation and imaging techniques, including pain roentgenography and sialography (Fig. 59-8). Calculi are frequently identified along the course of the involved duct by bimanual palpation of the floor of the mouth. Contrast studies are helpful for the identification of radiolucent stones that are associated with proximal duct dilatation and delayed emptying. Parotid sialoliths are most difficult to diagnose because they are frequently small, palpation is often impeded by the cheek tissues, and, in most instances, they are radiolucent (Suleiman and Hobsley, 1980).

Early management of salivary calculi is conservative, consisting of measures identical to those outlined for non-obstructive sialadenitis. Stones palpable near the ductal orifice can frequently be moved manually toward the orifice and removed. Vigorous probing should be avoided because it can initiate an inflammatory episode. If necessary, the ductal orifice can be incisionally enlarged to facilitate stone removal (Fig. 59-9). Sialodochoplasty of Stensen's duct has a high incidence of stricture, so temporary stenting with silastic tubing is necessary. Retained hilar calculi will continue to predispose the gland to repeated infection and ductal stricture and therefore should be treated by elective surgical removal of the gland. Other treatments, including low-dose irradiation, tympanic neurectomy, and ductal ligation, have proved to be ineffective.

## **Viral Infections of the Salivary Glands**

### **Viral diseases**

Viral involvement of the salivary glands most commonly occurs through hematogenous dissemination, although infection by retrograde ductal migration does occur. Viral infestation of salivary parenchyma is not always locally symptomatic, as transmission from blood to saliva occurs without localizing signs in many systemic viral infections including rabies, hepatitis, influenza, and poliomyelitis.

### **Mumps**

Mumps is the single most common cause of nonsuppurative acute sialadenitis, occurring primarily in children. Bilateral parotid gland swelling occurs in most cases, but submandibular gland swelling does occur in rare cases. Parotid gland inflammation is part of a generalized and highly contagious viral infection caused by a paramyxovirus. The virus is

endemic in the community and spreads efficiently by air-borne droplets from salivary, nasal, and urinary excretions. The incubation period averages 18 days, with illness onset signified by pain and swelling in one or both parotid glands. Progression of parotid gland swelling can be rapid and sufficient to cause displacement of the pinna. Pain is usually exacerbated by the physiologic stimulus of eating, which causes contractile ejection of saliva from the inflamed gland. Findings at the orifice of the parotid (Stensen's) duct are usually absent. Infective virus is shed through the saliva for up to a week following gland enlargement. Ductal epithelial desquamation may lead to secondary ductal obstruction and dilatation. Adults are rarely infected due to life-long immunity incurred by childhood exposure or MMR vaccination.

Proof of diagnosis can be obtained through hemagglutination inhibition and complement fixation tests but is rarely required given the characteristic features present in all but exceptional cases. Routinely obtained laboratory tests are usually unremarkable for occasional leukopenia. Elevations in serum salivary type isoamylase parallel the pattern and duration of glandular swelling. Histologic examination reveals substantial cytoplasmic vacuolization of acinar cells.

Generally, the symptoms of viremia, including low-grade fever, arthralgia, malaise, and headache, begin to abate within 3 to 7 days. The resolution of gland swelling usually requires several weeks, frequently proceeding asymmetrically. As with any viral illness, treatment is directed toward supplemental hydration and rest, with dietary modifications to minimize glandular secretory activity. More fulminant infections occasionally progress to include meningoencephalitis, orchitis, pancreatitis, and nephritis.

Acute viral parotitis also can arise from other less common endemic organisms including parainfluenza virus, coxsackievirus, echovirus, Epstein-Barr virus (EBV), and choriomeningitis virus.

### **Acquired immunodeficiency syndrome (AIDS)**

Infection with the human immunodeficiency virus (HIV) is frequently associated with lymphoproliferative and cystic enlargement of the major salivary glands, followed by salivary dysfunction (Finfer et al, 1988). This process, more recently termed *HIV-associated salivary gland disease (HIV-SGD)*, has been described among HIV-seropositive and high-risk but HIV-seronegative patients. Salivary gland involvement can be the initial manifestation of HIV disease, with the parotid glands being most frequently affected (DeVries et al, 1988). Bilateral cystic enlargement of the parotid glands has been observed in HIV-infected children, usually in combination with lymphocytic interstitial pneumonitis (Falloon et al, 1989). HIV is detectable in salivary secretions, but it is presently unknown whether salivary gland involvement is the result of direct infection or is simply a focal manifestation of the progressive generalized lymphadenopathy characteristic of the disease.

The clinical features of HIV-SGD include gradual non-tender enlargement of one or more salivary glands, with xerostomia due to compromised glandular secretion, frequently combined with dry eyes and arthralgia (Fig. 59-10). For this reason, the sicca complex symptoms accompanying this disease process have been likened to Sjögren's syndrome (SS) and have stimulated investigation of a possible common autoimmune etiology. Biopsy analysis reveals similar inflammatory infiltrate between SS and HIV-SGD, but the serologically

detectable antibodies associated with SS do not appear in HIV patients with salivary gland abnormalities (Schiedt et al, 1989). This suggests that HIV-SGD is either a separate entity or that the immune reaction is modified because of the nature of the disease. Other opportunistic infectious agents that have been implicated as possible causes have included the EBV and cytomegaloviruses (Couderc, 1987).

Histologic examination of excised glands shows numerous adjacent epithelium-lined cysts, up to several centimeters in size, that usually appear to have originated within the substance of the lymph node (Fig. 59-11). These are filled with macrophages and lymphocytes in a watery yellowish fluid containing cholesterol crystals and are surrounded by a dense lymphoid infiltrate with germinal centers (Ryan et al, 1985).

Appropriate management of these asymptomatic lesions may depend upon the patient's status at the time of diagnosis. Despite a clinical suspicion of HIV, these lesions probably should be treated like any incidental enlargement of the salivary gland; that is, by surgical removal and pathologic examination. This philosophy is supported by an underlying incidence of lymphoma in up to 10% of cases in one series of HIV patients (Ioachim et al, 1987). However, in the setting of documented HIV infection, other investigators have shown that the findings of needle aspiration and CT imaging are sufficiently typical to provide a presumptive diagnosis justifying conservative clinical observation of these lesions (Falloon, 1989).

### **Granulomatous Salivary Gland Infections**

Salivary gland involvement not infrequently arises as a manifestation of a chronic granulomatous disease involving the lymphatic network in and surrounding the parotid gland. Direct infiltration of the adjacent glandular parenchyma occurs in fulminant cases. Manifestations frequently feature asymptomatic gradual enlargement of a nodule within the gland substance, suggesting a neoplasm. Included among these diseases are mycobacterial diseases (tuberculous and atypical forms), actinomycosis, cat scratch disease (CSD), toxoplasmosis, and tularemia.

#### **Mycobacterial diseases**

Salivary gland involvement is included among the less commonly encountered forms of cervicofacial tuberculosis and nontuberculous mycobacterial infections. Gland involvement is characterized by indolent, painless enlargement mimicking the behavior of a slow-growing neoplasm.

*M. tuberculosis* infection of the major salivary glands can occur either through intraglandular lymph nodes or parenchymal infiltration. Salivary gland involvement can occur as a primary infection or as a recrudescence of an established pulmonary focus (Donohue and Bolden, 1961). Isolated salivary gland involvement is most common in the parotid gland, perhaps because of the intraglandular lymph nodes unique to this gland. Signs of prior active tuberculosis of the lung will usually be evident on chest radiographs. Affected patients will usually have constitutional signs including fever, night sweats, and weight loss. Facial nerve involvement is rare.

Nontuberculous mycobacterial (NTM) infections of the salivary glands are most frequently encountered in children from 16 to 36 months of age. Involvement caused by *M. bovis* has become much less common since the widespread pasteurization of milk, but exposure to infection continues to occur, possibly through ubiquitous warm water-fixture contamination by *M. kansasii*, *M. scrofulaceum*, and *M. avium-intracellulare* (Du Moulin et al, 1988). Lymph nodes in and adjacent to the parotid and submandibular glands are most frequently involved, and sinus tracts can drain to the skin (Fig. 59-12). The tuberculin skin test can be weakly positive. Chest radiographic findings and constitutional symptoms are usually absent. Diagnosis is usually based on strong clinical suspicion and exclusion of other causes because tissue staining and microscopic features are nonspecific and culture results require up to 6 weeks. Fine-needle biopsy is preferred to incisional biopsy, which can produce a fistula refractory to healing. Eradication of the disease with antituberculous drugs is usually not successful, so excision with preservation of the facial nerve remains the mainstay of treatment (Pransky et al, 1990; Waldman, 1982).

### **Actinomycosis**

Actinomycosis is an infectious disease caused by a gram-positive anaerobic organism. Actinomyces is a mouth and bowel commensal, which can rarely infect the major salivary glands. Actinomyces most often infects cervicofacial, ileocecal, and pulmonary sites. *Actinomyces israelii* is the most commonly encountered species, with the balance of cases attributable to *A. bovis* and *A. naeslundii*. In most cases, antecedent disease combined with trauma to the mucosa permits invasion of the organism, leading to a slowly progressive inflammatory reaction. Isolated salivary gland involvement probably occurs via retrograde ductal migration and primarily occurs in the parotid gland (Roveda, 1973). Involvement of the salivary glands also can occur as part of direct spread of an invasive cervicofacial infection.

Patients typically have a painless, indurated enlargement of the involved gland that may suggest a neoplasm. Facial nerve involvement has not been described. A history of recent dental disease and manipulation is common. Constitutional symptoms, malaise, leukocytosis, and lymphadenopathy are typically absent. Multiple draining cutaneous fistulas are characteristically the result of lymph node necrosis.

Diagnosis is facilitated by needle aspiration of the mass or a fistula swab with smears and stains to examine for the presence of sulphur granules and the organism. Sulfur granules have also been described for nocardiosis, but their identification in the presence of filamentous gram-positive rods is diagnostic for actinomycosis (Harris et al, 1985). Biopsy specimens show firm fibrous encasement of multiloculated abscesses containing whitish-yellow pus. Anaerobic cultures are obtained to confirm the diagnosis and for species identification.

Surgery for cervicofacial actinomycosis, except in the setting of isolated involvement, is mainly of diagnostic use because antibiotics are the mainstay of treatment. The antimicrobial of choice remains penicillin because Actinomyces is not known to be resistant to penicillin. Other acceptable alternatives include clindamycin, doxycycline, or erythromycin. Antimicrobial therapy should consist of a 6-week parenteral course followed by an additional 6 months of oral treatment to completely eradicate the organism (Hensher and Bowerman,

1985). Response to treatment is generally favorable, with cure rates approaching 90% despite a delayed diagnosis in most instances (Weese and Smith, 1975).

### **Cat scratch disease**

Cat scratch disease (CSD) is a granulomatous lymphadenitis that most commonly results from cutaneous inoculation caused by scratch trauma from a domestic cat. Recently, the infective organism has been cultured and characterized as a small, pleomorphic, nonacidfast gram-negative bacillus (Wear et al, 1983).

Most reported cases occur in the head and neck, frequently involving the skin and lymphatics in and around the parotid and submandibular glands. Lymph node involvement histologically shows reticular cell hyperplasia, granuloma formation, and microabscesses. As generalized inflammatory infiltration progresses, larger abscesses form by coalescence.

Usually systemic symptoms are mild or absent, and the reported incidence of 2000 annual cases in the USA may be a gross underestimation (Daniels and MacMurray, 1954). Yet, severe cases can progress to include encephalitis, arthritis, neuroretinitis, osteomyelitis, and hepatitis (Margileth et al, 1987).

Diagnosis is facilitated by a history of cat exposure or scratch injury combined with a positive Hanger-Rose skin test. Staining of biopsy specimens with Warthin-Starry silver usually identifies the intracellular bacilli.

There is no specific treatment for CSD. Adenopathy generally resolves within a few months, but node aspiration can apparently have diagnostic and therapeutic benefit (Spires and Smith, 1986).

### **Toxoplasmosis**

Toxoplasmosis, an uncommon disease in the USA, is caused by the organism *Toxoplasmosis gondii*. The usual host of this organism is the domestic cat. Parotid gland disease can involve singular or multiple intraparotid or periparotid lymph nodes. The organism exists in trophozoite, cyst, and oocyst forms, with the latter only existing in the feline vector. Trophozoites or cysts gain entrance to the human host most often through ingestion of infected and undercooked lamb, beef, or chicken, or, less commonly, through cat feces. Digestion of the cyst capsule then permits widespread hematogenous dissemination and multiplication of trophozoites in virtually all lymphoreticular organs.

Both disseminated and lymphadenopathic forms of the disease have been described. Immunocompromised individuals are most at risk for the disseminated form of the disease, which features myalgia, lethargy, and anorexia combined with hepatosplenomegaly, pericarditis, and myocarditis. Alternately, the lymphadenopathic variety occurs much more commonly, with the vast majority of patients presenting with isolated cervical lymphadenopathy (Rafaty, 1977).



Definitive diagnosis can only rarely be provided by isolation of the organism. Confirmation of a presumptive histologic diagnosis is made by acute and convalescent serologic testing (Frenkel, 1985). Chemotherapy is generally reserved for obviously progressive infections or those involving pregnant or immunocompromised individuals and consists of the combined administration of pyrimethamine and trisulfapyridine.

### **Tularemia**

Tularemia is caused by the gram-negative organism *Franciscella tularensis*, which is typically transmitted to humans by insect vectors such as ticks or deer flies, handling of infected animal tissues, and aerosol inhalation (Foshay, 1950). The cottontail rabbit has been a principal host in North America, but throughout the world the organism has been isolated in many animal species. In most cutaneously transmitted cases, a reddish papulae forms at the site of entry. This may occur in the region of the parotid gland. Following a 2- to 10-day incubation period, neighboring and draining lymph nodes become enlarged, tender, and inflamed. Headache, fever, and other toxic signs can occur. If infectious entry was via gastric or pulmonary routes, a skin lesion will not be detected and lymphatic involvement may be more diffuse. Despite phagocytization within the reticuloendothelial organs, the infecting organism can remain viable intracellularly, stimulating a chronic granulomatous disease.

The disease is treated with parenteral aminoglycosides such as streptomycin or gentamicin with tetracycline being a suitable alternative. Aggressive manipulation of fluctuant nodes during the acute phases of the infection is discouraged because this may disseminate the infectious agent systemically. Following an interval of antibiotic therapy and the resolution of systemic symptoms, fluctuant buboes, likely to contain sterile fluid, can be safely incised or drained.