Tuberculous Lymphadenitis and Parotitis

JUAN CARLOS CATAÑO1 and JAIME ROBLEDO2

1Section of Infectious Diseases, University of Antioquia Medical School, Medellín, Colombia; 2Section of Mycobacteria Research, Corporación para Investigaciones Biológicas and Universidad Pontificia Bolivariana, Medellín, Colombia

ABSTRACT Tuberculous lymphadenitis is the most common extrapulmonary manifestation of disseminated tuberculosis (TB). It is considered to be the local manifestation of the systemic disease that has disseminated to local lymph nodes, but a high index of suspicion is needed for the diagnosis, because there are several infectious and noninfectious diseases that can mimic the same clinical picture. In recent years, different diagnostic methods have been introduced, including fine-needle aspiration cytology, which has emerged as a simple outpatient diagnostic procedure that replaced the complete excisional node biopsy, and a number of molecular methods which have greatly improved diagnostic accuracy. This chapter covers the most actual knowledge in terms of epidemiology, clinical manifestations, pathogenesis, and treatment and emphasizes current trends in diagnosis of tuberculous lymphadenitis. TB parotid gland involvement is extremely rare, even in countries in which TB is endemic. Because of the clinical similarity, parotid malignancy and other forms of parotid inflammatory disease always take priority over the rarely encountered TB parotitis when it comes to differential diagnosis. As a result, clinicians often fail to make a timely diagnosis of TB parotitis when facing a patient with a slowly growing parotid lump. This chapter highlights the most important features of this uncommon disease.

HISTORICAL REVIEW: KING’S EVIL AND THE ROYAL TOUCH

Tuberculosis (TB) of the lymphatic glands has afflicted humans for thousands of years. Scrofula is usually a term used to describe the swelling of the lymph nodes in the neck caused by TB; the name scrofula was given because pigs were considered susceptible to the disease, and it comes from the Latin scrofulae, meaning brood sow. Hippocrates (460–377 BC) mentioned scrofulous tumors in his writing, and Herodotus (484–425 BC) described the exclusion of those afflicted with leprous or scrofulous lesions from the general population. In the Middle Ages, it was believed in England and France that a touch from royalty could heal skin disease known as scrofula or the “king’s evil.” The practice began in the 11th century in France with Robert the Pious (970–1031), King of France, and in England with King Edward the Confessor (1003–1066). Subsequent English and French kings were thought to have inherited this royal touch, which was supposed to show that their right to rule was God given. In grand ceremonies, kings touched hundreds of people afflicted by scrofula (1).

By the late 1400s, it was believed that one could also be cured by touching a type of coin called an angel, which had been touched by the monarch. After angels ceased to be minted in the 1620s, the same effect was said to be achieved by touching a gold medallion embossed much like the old coin. Some monarchs touched many people; King Henry IV of France touched up to 1,500 victims during one event. The last English monarch to carry out this practice was Queen Anne, who died in 1714, but it continued in France. Louis XV touched more than 2,000 scrofula victims, and the practice ended entirely under King Charles X (1757–1836) of France (2).
Many medieval physicians believed that scrofula resulted from gluttony and therefore recommended a restrictive diet and avoidance of “all things that fill the head with fumes,” such as garlic and onions, strong wine, shouting, worry, and anger. Medical treatment often consisted of a plaster of lily root, unripe figs, bean flour, and nettle seed. Attempts might be made to rupture the lesions with the help of blister beetles. Surgery consisted of incision of the scrofulous node, scraping away and clamping of the flesh overlying it, and removal of any attached nodes (3).

TB as a distinct disease was identified by the early 1800s, thanks to pathologic findings by Laennec and Schönlein, showing multiple sites of characteristic granulomatous lesions with caseous necrosis, cavitation, and fibrosis (4), but it was only in March 1882 in Berlin, Germany, when Robert Koch (1843–1910) announced one of the most important discoveries in the history of humankind—the identification of the cause of TB, the bacterium later termed Mycobacterium tuberculosis—that the beginning of a new era in terms of the microbiology of this new-old disease was marked (5). The following century witnessed a steady decline in TB due to mass X-ray screening, the development of drug therapy, Mycobacterium bovis BCG immunization, improvements in socioeconomic factors, and possibly the gradual acquisition of resistance to infection by the population as a whole; however, the latter part of the 20th century witnessed a steady resurgence of the disease, due to its synergism with the human immunodeficiency virus (HIV) global pandemic (6).

MICROBIOLOGY: SOMETHING ABOUT THE BUG

The term tubercle bacilli refers to two species from the Mycobacteriaceae family: Mycobacterium tuberculosis and Mycobacterium bovis, which are the most common species in the M. tuberculosis complex. This complex also includes M. microti, a pathogen of rodents, rarely found in humans; M. africanum and M. canetti, responsible for sporadic disease in humans; and M. pinnipedii and M. caprae, which cause disease only in animals (7, 8).

M. tuberculosis has a curved structure 0.3 to 0.6 μm wide by 1 to 4 μm long and is a slow-growing facultative intracellular pathogen that can survive and multiply inside macrophages and other mammalian cells. It has a generation time of 15 to 20 h, compared with less than an hour for many of the pyogenic bacteria that cause disease in humans. The colonies are brown, dry, and rough in appearance and are usually visible between 4 and 6 weeks when grown in regular medium culture rich in lipids. It differs from other species of mycobacteria by conventional biochemical tests like niacin accumulation, cord factor formation, nitrate-to-nitrite conversion, growth inhibition by paranitrobenzoic acid, and the absence of pigment production. Similarly, the M. tuberculosis complex species can be differentiated by several morphological and biochemical tests (9). A characteristic feature of M. tuberculosis is the complexity of its outer sheath, which is essential in the relationship established by the microorganism with the immune system of its host. The main components of this envelope, particularly rich in lipids but also in carbohydrates and proteins, act as antigens and structural elements, and some of them are secreted into the medium in which the microorganism is grown (10).

Knowledge of the genetic characteristics and molecular biology tools has enabled the design of methods to differentiate several species of mycobacteria, including DNA-specific probes, PCR, and restriction fragment length polymorphism analysis (8). These methods shorten the identification time compared to those obtained by conventional methods; however, most of them do not differentiate between the species of the M. tuberculosis complex. The M. tuberculosis genome, sequenced in 1998, consists of approximately 4,000 genes, of which 6%, about 200, encode enzymes related to lipid synthesis, demonstrating the importance of such substances for these microorganisms. Other important groups of genes are related to the intermediary metabolism and respiration (22%), with the synthesis of the cell wall and other cellular processes (13%), leaving 30% to 40% of the genome still with unknown function (10, 11).

EPIDEMIOLOGY: HOW DOES THE WORLD LOOK?

TB is a huge problem worldwide; in 1993, it was declared by the World Health Organization (WHO) as a global emergency. Nowadays it is the leading cause of death globally due to an infectious agent, with more than 90% of cases and deaths occurring in underdeveloped countries. In 2014, TB killed 1.5 million people (1.1 million HIV negative and 0.4 million HIV positive). Worldwide, 9.6 million people are estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women, and 1.0 million children. Globally, 12% of the 9.6 million new TB cases in 2014 were in HIV-positive persons (12). Of the 9.6 million new TB cases
in 2014, 58% were in the Southeast Asia and Western Pacific regions. The African region had 28% of the world’s cases in 2014: 281 cases for every 100,000 people, more than double the global average of 133. India, Indonesia, and China also had a huge number of cases: 23%, 10%, and 10% of the global total, respectively (12).

HIV-TB coinfection and the increasing drug resistance are the greater threat to achieving future control of the disease. Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases are multidrug-resistant TB, a level that has changed little in recent years (12). In 2014, an estimated 1.2 million (12%) of the 9.6 million people who developed TB worldwide were HIV positive. Persons in the African region accounted for 74% of these cases. The number of people dying from HIV-associated TB peaked at 570,000 in 2004 and had fallen to 390,000 in 2014 (a 32% decrease). Globally, 51% of notified TB patients had a documented HIV test result in 2014, a small increase from 49% in 2013 (12).

An increasing incidence of extrapulmonary TB, resulting in an increasing incidence of tuberculous lymphadenitis, has been noted both in developing and developed countries since the mid-1980s. The incidence of extrapulmonary TB in the United States is 5.4%, and TB lymphadenitis comprises 30 to 50% of these cases (13). In India, extrapulmonary TB comprises 20% of all TB cases, and TB lymphadenitis is seen in nearly 35% of extrapulmonary cases, with cervical lymph nodes involved in 60 to 90% of cases (14). Extrapulmonary TB has become more common since the advent of HIV infection. Extrapulmonary involvement can be seen in more than 50% of patients with concurrent HIV and TB infections (15). In 2014, the extrapulmonary TB notifications reached over 1.5 million cases around the globe (12), and a higher incidence of TB lymphadenitis has been noted in countries with a high prevalence of both TB and HIV, but in developed countries with low TB prevalence, it is more often seen in immigrants and those who travel to countries of higher prevalence (16, 17).

Historically, lymph node TB has been identified most commonly in children; however, in recent years, lymphadenitis became common in persons between 20 and 40 years of age and has exhibited female predominance, but the age distribution reflects the degree of ongoing transmission in a given population. Disease in the elderly is generally due to reactivation of infection acquired in the remote past, whereas TB in young children indicates ongoing active transmission in the community (18). The reason for the association of female sex with tuberculous lymphadenitis is not well understood, but one study found a difference in tumor necrosis factor and interleukin-10 production between the sexes, thus suggesting that this difference may play a role in susceptibility (19); however, another study suggested additional factors to explain this difference between the sexes, including CD4+ lymphocyte counts, endocrine factors, socioeconomic factors, and cultural factors (20).

As of 2016, the goal is to end the global TB epidemic by implementing the End TB Strategy. Adopted by the WHO assembly in May 2014 and with targets linked to the newly adopted sustainable development goals, the strategy serves as a blueprint for countries to reduce the number of TB deaths by 90% by 2030 (compared with 2015 levels) and cut new cases by 80% (12).

PHYSIOPATHOLOGY: HOW DOES IT WORK?

The entryways of the tubercle bacilli are inhalation, ingestion, and direct inoculation. The most important is the inhalation of infectious particles expelled by individuals with pulmonary TB (smear-positive patients), coughing, talking, or sneezing. Larger particles of 5 to 10 μm are retained in the nose, but those less than 5 μm can avoid mechanical barriers of the respiratory tract and penetrate into the lung alveoli; each of these small particles can carry from 1 to 5 bacilli, sufficient to establish an infection, and they can also stay in room air and be infectious even after the patient has left the room. The main determinant for the risk of infection is close contact with highly infectious individuals, such as patients with smear-positive pulmonary TB; however, it is estimated that between 10% and 20% of cases are transmitted by smear-negative patients (21).

When the population of activated T cells reaches a certain size, the delayed tuberculin hypersensitivity becomes positive, generally between the third and ninth weeks after initial infection. Granuloma formation is the most important immunopathological response in M. tuberculosis infection; in this process, the natural killer cells and neutrophils recruited play a pivotal role: this formation correlates with the development of hypersensitivity, improved phagocytosis, and cell death by the macrophage. The granuloma plays an important role in organizing the interaction between immune cells, leading to an effective response that inhibits and kills the bacilli, contains the infection, prevents the spread of the organism, and locates the inflammatory response and tissue damage (22). But granulomatous lymphadenitis does not always mean TB: actually, there are several infectious and noninfectious conditions that have

Tuberculous Lymphadenitis and Parotitis
to be considered in the differential diagnosis according to local epidemiology: sarcoidosis, berylliosis, toxoplasmosis, syphilis, cat scratch disease, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, brucellosis, and infection with nontuberculous mycobacteria (23).

There are several risk factors related to the development of active disease, especially forms of extrapulmonary TB. HIV is the highest risk factor, where extrapulmonary TB is commonly seen when CD4 counts are below 300/mL, often in those patients with CD4 counts less than 100 cells/mL. In HIV-infected patients, tuberculous lymphadenitis can also occur in association with pulmonary and/or miliary disease (24). Other important risk conditions are malnutrition, alcoholism, diabetes mellitus, and smoking, which can increase two to three times the risk of developing the disease (25). Other risk factors are hematologic malignancies, silicosis, gastrectomy, and treatment with steroids and immunosuppressive medications (26). Similarly, administration of monoclonal antibodies directed against tumor necrosis factor, used for the treatment of chronic inflammatory diseases, significantly increases the risk of developing the disease in individuals with latent TB (27), especially in countries with a high burden of infection (28).

The infection of lymph nodes by mycobacteria occurs either through hematogenous dissemination following primary TB or as a local extension from tuberculous infection of the tonsils or adenoids (29). It is well accepted that M. tuberculosis can migrate from the primary infection site (lungs) to the lymphatic system and bloodstream. However, the detailed mechanisms of bacterial dissemination remain unclear. To migrate from the lungs to the draining lymph nodes and bloodstream, the bacilli must break through the alveolar epithelium. So far, some evidence has shown that bacteria inside alveolar macrophages or dendritic cells can be relocated by these professional phagocytes into lymph nodes and blood. Bacteria could also invade and lyse epithelial cells after infecting epithelial cells (30). From the regional nodes, organisms may continue to spread via the lymphatic system to other nodes or may pass through the nodes and reach the bloodstream in small numbers, from which they may spread to virtually any organ in the body. This form of lymphatic and hematogenous dissemination is usually self-limited, and more than 90% of primary infections in humans heal without symptomatic disease, but in the remaining 10%, the infection progresses, becoming clinically significant (31).

**CLINICAL MANIFESTATIONS: HOW DOES IT LOOK?**

Clinical presentation depends on the lymph nodes involved. TB lymphadenitis in cervical, axillary, and inguinal areas can present as nontender swelling without significant systemic symptoms. Cervical node involvement predominates in over two-thirds of TB adenitis cases (32). It is often unilateral, involving one or more nodes of the anterior and posterior cervical chain (Fig. 1). Occasionally, submandibular and supraclavicular nodes are affected. Other sites of lymph node involvement include axillary, inguinal, intra-abdominal (mesenteric and para-aortic), and intrathoracic lymph nodes (33). The lymph nodes are generally firm and discrete at the onset and become fluctuant and matted as the disease progresses. TB lymphadenitis can also present as a tender mass with involvement of a single node. Occasionally (10% of cases), draining sinuses are noted (Fig. 2).

Compression of adjacent organs by the enlarged nodes may lead to symptoms such as dysphagia from esophageal compression by intrathoracic nodes, jaundice and portal vein thrombosis from hepatic lymph nodes, and small-bowel obstruction from mesenteric nodes (34). The affected nodes may also erode into adjacent organs, resulting in draining sinuses, empyema, and esophageal perforation (Fig. 3). Constitutional symptoms such as fever, weight loss, fatigue, and occasional night sweats are often present in HIV-coinfected patients, in contrast to non-HIV patients (24). There is a history of tuberculous contact in 21.8% of patients and active tuberculous infection compromising other organs in 16.1% of the cases, but reinfection can occur any time after the primary infection through either reactivation of the endogenous source of primary infection or contamination by an exogenous source (35).

**MICROBIOLOGICAL DIAGNOSIS: HOW TO FIND IT**

It is considered that excisional biopsy has high sensitivity when cultured for diagnosis of TB lymphadenopathy (36, 37); however, this procedure is invasive and not available in low-resources areas and so is recommended only in cases when the initial diagnosis is not conclusive or if there is no remission of symptoms despite adequate antibiotic treatment (38). Fine-needle aspiration biopsy (FNAB) is a much less invasive procedure that provides a good clinical specimen suitable for initial pathologic study (39). Several studies have demonstrated the utility of FNAB in TB lymphadenopathy diagnosis (40–42),
but one of the pitfalls of FNAB is the amount of material obtained for microbiological studies, which may negatively affect the performance of these methods in diagnosis of tuberculous lymphadenitis (43); it is recommended that FNAB samples be processed for cytology and microbiological studies, since the combination of both procedures increases the sensitivity for TB lymphadenitis diagnosis (44).

As in many other types of TB, tuberculous lymphadenitis needs to be diagnosed by isolating the bacillus or identifying its DNA from the clinical sample. Culture remains the “gold standard” for diagnosis, but it may take up to 3 to 4 weeks to render a positive result; however, rapid culture methods can give results as rapidly as 1 to 2 weeks (45), even though culture sensitivity may be as low as 50%, depending on the type of specimen, i.e., excisional biopsy specimen versus FNAB specimen (46). An inverse relationship between the presence of granulomas and isolation by culture has been described: higher culture rates and smear positivity have been found in lesions where necrosis was predominant (83.3%), compared to 50% in granulomatous lesions (32).

Tuberculous lymphadenitis is a paucibacillary form of TB. The sole use of acid-fast bacillus (AFB) smear for diagnosis exhibits a low sensitivity, but the use of a fluorescent light-emitting diode microscope may increase the sensitivity of AFB smear in FNAB samples from 25% to 45% compared to that of cultures (47). Other studies have compared the performance of AFB detection by using Ziehl-Neelsen stain, auramine-rhodamine stain, and mycobacterial autofluorescence in Papanicolaou-stained lymph node aspirates; the last technique shows sensitivity and specificity comparable to those of the other stained smears (48, 49), and when combined with cytopathology, it may be the faster initial diagnostic method for lymphadenitis in areas where TB is endemic (50).

Cytomorphologic findings in clinical samples do not alone confirm the presence of M. tuberculosis, but cytomorphologic examination has been used extensively for diagnosis of tuberculous lymphadenopathy due to its easy process, low cost, and rapid results, particularly when it is done in smears obtained by FNAB. Cytology diagnosis of TB lymphadenopathy can be performed using several stains, such as Giemsa, Wright, hematoxylin-eosin, or Papanicolaou. The diagnosis of TB is frequently made on the basis of findings such as epithelioid granulomatous reaction, accompanied or not by caseation and necrosis (40, 51). For others, nonspecific lymphoid infiltrates,

**FIGURE 1 (A)** Multiple cervical lymphadenopathy in a patient with TB lymphadenitis. **(B)** Computed tomography showing diffuse lymphadenopathy in cervical chains.
noncaseating granulomas, or Langerhans giant cells in areas of caseous necrosis are enough to support a diagnosis of probable TB (36). A useful scale to grade cytomorphologic changes has been described as follows: grade I, epithelioid granuloma reaction with caseation; grade II, epithelioid granulomatous reaction without caseation; grade III, nongranulomatous reaction with necrosis; grade IV, nonspecific; grade V, inadequate sample. Grades I, II, and III are considered highly suggestive of TB (41).

Among the different molecular technologies used for diagnosis, nucleic acid amplification with the further identification of specific genome material by PCR had been established as an alternative complementary method for diagnosis in different infectious diseases. In general, published data concerning PCR for diagnosis of tuberculous lymphadenitis, by either in-house methods or commercial ones, show a performance very similar to those of microbiological methods such as culture and in some cases even increase the performance of those, identifying more positive patients (52); however, there are differences in diagnostic accuracy influenced by the type of population studied, type of clinical specimen, the gene target used for amplification, and the type of PCR method utilized (43, 53–55). Gene Xpert MTB/RIF (Cepheid, Sunnyvale, CA) is a more recently introduced commercial type of molecular method based on real-time PCR; it allows detection of 
M. tuberculosis complex and confirmation of rifampin (RIF) resistance at the same time. This test was initially endorsed by WHO in 2010 and updated for diagnosis of pulmonary and extrapulmonary TB in 2013 (56). The WHO policy stated that Gene Xpert MTB/RIF may be used as a replacement of conventional methods for diagnosis of tuberculous lymphadenitis, being a conditional recommendation with a very low quality of evidence (56). A couple of studies evaluated Gene Xpert for diagnosis of extrapulmonary TB in countries where TB was nonendemic (57) and endemic (58); the sensitivity with FNAB compared to culture in both studies was over 80%, and the specificity varied according to the setting, being 99 to 100% in the country where TB was nonendemic and 78% in the one where it was endemic. In both studies there were samples culture positive and Gene Xpert negative and samples culture negative and Gene Xpert positive, emphasizing the need, when resources are available, to perform both methods to increase the yield for diagnosis of tuberculous lymphadenitis.

In countries with low endemicity, the tuberculin skin test may add some useful information for diagnosis of tuberculous lymphadenitis; however, high rates of tuberculin skin test positivity have also been described in

**FIGURE 2** (A) Cervical scrofula. (B) Sternal scrofula. Reprinted from reference 106, with permission.
low-endemicity countries in association with immigrants (32), as well as in native populations (59). At least one-third of tuberculous lymphadenitis patients have an abnormal chest X-ray, and 15% have a positive culture sputum (32), underlining the need for studies that may confirm a concomitant intrathoracic compromise of the lungs. Neck ultrasonography is a useful imaging diagnostic tool in the initial assessment of lymph nodes, allowing the identification of either solid or cystic masses and for guiding needle aspiration (60, 61); it has been used for diagnosis of tuberculous lymphadenitis based on imaging features, like poorly defined anechoic areas with or without sinus and abscess formation and avascular areas with displaced vascularity, which have a high sensitivity and negative predictive value but low specificity (62).

TREATMENT: HOW TO DEAL WITH THIS
The principles underlying the treatment of pulmonary TB also apply to extrapulmonary disease, including lymphadenitis. The objectives of TB therapy are to rapidly reduce the number of actively growing bacilli in the patient, to eradicate populations of persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy, and to prevent selection of drug-resistant bacilli during therapy (63). To maximize completion of therapy, management strategies should utilize a broad range of approaches; among these, directly observed therapy, the practice of observing patients swallow their anti-TB medications, has been widely used as the standard of practice in many TB programs. Directly observed therapy has been significantly associated with improved treatment success (the sum of patients cured and patients completing treatment) and is useful for early recognition of adverse drug reactions and treatment irregularities, remaining the standard of practice in the majority of TB programs around the globe (64).

Chemotherapy for lymphadenitis TB is initiated with a 4-drug regimen of isoniazid (INH), pyrazinamide, RIF, and ethambutol, which remains the preferred initial treatment for drug-susceptible tuberculosis. For TB strains known or presumed to be susceptible, after 2 months of 4-drug therapy, pyrazinamide and ethambutol may be discontinued and INH and RIF continued during a continuation phase. The opinion of experts is that the preferred frequency of dosing for extrapulmonary TB is once daily for both the intensive and continuation phases. No randomized controlled trials have studied intermittent drug administration for extrapulmonary TB (65). Pyridoxine (vitamin B6) is given with INH to all persons at risk of neuropathy: pregnant women; HIV-positive patients; diabetic patients; patients with alcoholism, malnutrition, or chronic renal failure; and elderly patients (66).

A 6-month regimen is adequate for initial treatment of all patients with drug-susceptible tuberculous lymphadenitis (65), but affected lymph nodes may enlarge and new nodes can appear during or after therapy without any evidence of bacteriological relapse, a phenomenon known as the paradoxical response/reaction (67). Ther-
apertic lymph node excision is not indicated except in unusual circumstances (68). For large lymph nodes that are fluctuant and appear to be about to drain spontaneously, aspiration has been reported by some experts to be beneficial, although this approach has not been examined systematically. Incision and drainage techniques applied to cervical lymphadenitis, however, have been reported to be associated with prolonged wound discharge and scarring (69). Response to treatment in extrapulmonary diseases is often judged on the basis of clinical findings, because bacteriological evaluation is often limited by the difficulty in obtaining follow-up specimens.

For patients who have diabetes, HIV infection, extensive disease, or any immunosuppressive condition, expert opinion is to extend the continuation phase with INH and RIF for an additional 3 months, corresponding to a total of 9 months of therapy (65, 70, 71). When interruptions occur, the person responsible for supervision must decide whether to restart a complete course of treatment or simply to continue as intended originally. In general, the earlier the break in therapy and the longer its duration, the more serious the effect and the greater the need to restart treatment from the beginning (65).

Treatment of TB in patients with HIV infection has several important differences from treatment of patients who do not have HIV infection. The need for antiretroviral therapy, the potential for drug-drug interactions (especially between the rifamycins and antiretroviral agents), paradoxical reactions that may be interpreted as clinical worsening, and the potential for developing resistance to rifamycins when using intermittent TB therapy are some of these differences (65, 71). Patients with HIV and TB should start antiretroviral treatment around 2 weeks after starting daily anti-TB medications, in an effort to avoid immune reconstitution inflammatory syndrome (72, 73), which is seen in 14.4% of HIV-positive patients, compared with only 3.8% of HIV-negative patients (74).

**PAROTITIS: SOMETHING TO KEEP IN MIND**

TB parotid gland involvement is extremely rare, even in countries in which TB is endemic. Because of the clinical similarity, parotid malignancy and other forms of parotid inflammatory disease always take priority to the rarely encountered TB parotitis when it comes to differential diagnosis. As a result, clinicians often fail to make a timely diagnosis of TB parotitis when facing a patient with a slowly growing parotid lump (75, 76).

Although TB parotitis was first reported by von Stubenrauch in 1894 (77), only a limited number of cases of this infectious disease entity have been reported in the literature (78–94). Hence, it has been largely overlooked, and nowadays TB parotitis is no longer mentioned in the major textbooks of general medicine and infectious diseases. Clinicians’ limited awareness of TB parotitis will tend to lead to a missed or delayed diagnosis, and inappropriate treatment could result in gland destruction and even death (95–100).

Primary TB is often self-limited if the host’s immunity is sufficiently competent. However, hematogenous and/or lymphatic dissemination may result in the seeding of multiple organs and may therefore establish latent foci that become niduses for a delayed reactivation. The pathogenesis of TB parotitis remains unclear. The possible mechanisms of TB parotitis include hematogenous spread of *M. tuberculosis* from a distant primary lung focus, ascending infection from the prior infected cervical lymph nodes via a lymphatic route, seeding of the parotid gland by the sputum from current or prior pulmonary TB (92, 101), and adjacent spread from lymphatic nodes as a primary focus. There are two pathological forms of TB parotitis: the common localized form is due to involvement of intraglandular/periglandular lymph nodes, while the rare diffuse form, involving parenchyma, may be secondary to the nodal infection (92, 102).

Most patients with parotid TB do not have chest radiographic evidence of either active or prior pulmonary TB (78–80, 82, 83, 91, 92) but have concurrent cervical TB, and the main symptom is gland swelling (81, 84, 87, 90, 93). This observation suggests that TB parotitis results from *M. tuberculosis* invasion via either a lymphatic route to the glandular lymph nodes or spread from an adjacent focus. Tuberculous parotitis usually has an insidious and indolent clinical course and may exist for many years without causing systemic inflammatory response in a host (85, 86, 88, 89, 94–100). However, when the host’s immunity is attenuated, the affected site will rapidly and unrelentingly enlarge. TB parotitis frequently affects patients between the ages of 30 and 50 years, regardless of gender. A small number of patients developed draining sinus (77, 90) from the parotid gland and ipsilateral facial palsy (80, 84); these signs mimicked those of malignancy and thereby led to failure in making a prompt diagnosis.

There are two clinical forms of tuberculous parotitis: an acute tuberculous sialadenitis, which presents with diffuse glandular enlargement, and chronic sialadenitis, which manifests as an asymptomatic localized lesion...
within the parotid gland, slowly growing in size for many years; this should be differentiated from malignant neoplasms, chronic lymphadenitis, Sjögren’s syndrome, sialosis, and chronic or acute supplicative parotitis (75, 76). Malignancy is the most common preoperative misdiagnosis made in patients with TB parotitis. Because fine-needle aspiration cytology is a relatively safe and well-tolerated procedure, it can provide a preoperative diagnosis and should be performed first in patients with a parotid mass, especially those with a chronic clinical course; thus, unnecessary surgery can be avoided (103–105). There are no published trials of therapy for parotitis, so guidelines for TB affecting other organs should be followed (65).

CONCLUSIONS: SOME PEARLS TO REMEMBER

- Cervical tuberculous lymphadenitis usually presents with unilateral, multiple, matted neck swelling in young adults.
- Mycobacterial lymphadenitis, which is also referred to as scrofula, may be a manifestation of a systemic tuberculous disease or a unique clinical entity localized to the neck.
- Lymphadenitis TB can result from direct extension or hematogenous spread of the infection.
- The incidence of mycobacterial lymphadenitis has increased in parallel with increases in the incidence of mycobacterial infection and HIV worldwide.
- Mycobacterial lymphadenitis remains a diagnostic and therapeutic challenge because it mimics other pathologic processes and yields inconsistent physical and laboratory findings.
- It is important to differentiate tuberculous from non-tuberculous mycobacterial cervical lymphadenitis because their treatment protocols are different.
- Tuberculous adenitis responds well to anti-TB drugs, and surgery has a limited role in the treatment.
- Tuberculous parotitis is an overlooked entity in the evaluation of patients with a solitary mass in the parotid gland in the absence of history of TB.
- Physicians should have a high index of suspicion for TB parotitis when facing a middle-aged patient with a chronic parotid lump, even if the chest radiographs appear normal.
- Antimicrobial treatment of tuberculous adenitis and parotitis is the same as for TB affecting other organs.

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