

Scrofula

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Overview of Scrofula

Scrofula, the Latin word for brood sow, it is the term applied to tuberculosis (TB) of the neck. Tuberculosis is the oldest documented infectious disease. In the United States, pulmonary tuberculosis accounts for most tuberculosis cases. Cervical tuberculosis is usually a result of an infection in the lymph nodes, known as lymphadenitis. Extrapulmonary tuberculosis, such as scrofula, is observed most often in individuals who are immunocompromised.[1]

Scrofula has been known to afflict people since antiquity, and during the Middle Ages, the king's touch was thought to be curative. In modern times, surgery has played a pivotal role in the diagnosis and treatment of scrofula. Over the past several decades, however, surgical intervention has played a decreasing role because it has been fraught with persistent disease and complications. As in pulmonary tuberculosis, antituberculous chemotherapy has become the standard of care for scrofula, and newer diagnostic techniques (eg, fine-needle aspiration) have replaced more invasive methods of tissue harvesting.

Today, approximately 95% of mycobacterial cervical infections in adults are caused by *Mycobacterium tuberculosis*, and the remainder are caused by atypical mycobacterium, or nontuberculous mycobacterium (NTM). In children, this trend is reversed, with 92% of cases due to atypical mycobacterium.

NTM was first recognized as a cause of cervical adenitis in 1956. More than 50 species have now been identified, of which one half are recognized as pathogenic. Statistics indicate an increase in the prevalence and isolation of cervical lymphadenitis caused by NTM, far outnumbering tuberculosis as the cause of chronic cervical adenitis in children. The distinction has both diagnostic as well as therapeutic implications. Historically, scrofula was a term used to describe tuberculosis adenitis; however, NTM adenitis is included in the following text for completeness.

Pathophysiology of Scrofula

Mycobacterium tuberculosis is an obligate aerobe, non-spore-forming, slender rod. Humans are its only reservoir. Transmission is from person to person via respiratory route by inhalation of small aerosols. After a short period of replication in the lungs, silent dissemination occurs through the lymphohematogenous system to extrapulmonary sites, including the cervical lymph nodes.

A study by Bruzgielewicz et al of patients with head and neck tuberculosis found that among the 26 patients with lymph node tuberculosis, 15 patients had infected lymph nodes of the second and third cervical regions and 11 had infected lymph nodes of the first cervical region.[2]

Nontuberculous mycobacterium (NTM) differs from *M tuberculosis* in 2 respects: person-to-person transmission generally does not occur, and NTM species are ubiquitous in nature and not necessarily pathogenic or equated with disease. The oral cavity may serve as a common portal of entry because the disease primarily occurs in children who have a propensity to put contaminated objects in their mouth.

Epidemiology of Scrofula

Lymphadenitis is the primary manifestation of tuberculosis (TB) in 5% of the immunocompetent population, with the cervical lymph nodes providing the site of infection in two thirds of cases. In people with human immunodeficiency virus (HIV), cervical lymphadenitis may represent one third of the total presentations.

Starting in the mid-1980s, the first increase in incidence since 1882 was seen in the United States, the result of increased immigration from endemic countries, the rising population of persons infected with HIV, worsening urban social conditions, and the abandonment of rigid TB control programs.

A retrospective study by Qian et al examining the epidemiology of head and neck TB (HNTB) in Texas found that cervical lymphadenopathy was diagnosed in the majority of patients (96.9%), with the greatest incidence of HNTB being among females (52.7%) and in the 25- to 44-year age group (47.3%). Euro-American L4 was the most prevalent M tuberculosis lineage (52.3%) in patients with HNTB exclusively, with Indo-Oceanic L1 (21.5%) and East-Asian L2 (13.1%) being the second and third most prevalent in these individuals. Compared with patients who had HNTB exclusively, those with both HNTB and concurrent pulmonary involvement were more likely to be coinfecting with HIV, to be homeless, to have excessively used alcohol within the previous 12 months, and to engage in drug use.[3]

Currently, 2-10% of mycobacterial infections in the United States are due to other nontuberculous mycobacteria (NTM).

In impoverished countries where tuberculosis is endemic, TB continues to be a major health concern.

Using fine-needle aspiration cytology (FNAC), a retrospective, observational study from Pakistan, by Hashmi et al, found tuberculous lymphadenitis to occur more often in the cervical lymph nodes than in the axillary and inguinal lymph nodes. The investigators also observed that tuberculous lymphadenitis was more common in patients who were middle-aged or older. The report included 559 cases in which FNAC was carried out.[4]

The mortality for TB approaches 20% with multidrug-resistant pulmonary tuberculosis. Statistics are not available for isolated cervical lymphadenitis.

Recent statistics for NTM indicate an increase in prevalence and isolation of cervical lymphadenopathy caused by NTM. Because NTM is not generally reportable, the true incidence is difficult to determine.

Incidence of TB is increased in indigent, Asian, Hispanic immigrant, Native American, and Eskimo populations. People of all races are affected with NTM, with a white predominance.

For TB, the female-to-male ratio of is 2:1, and it affects people of all ages . For NTM, the female-to-male ratio is 1.3:1, but NTM affects children aged 1-5 years.

Clinical Manifestations of Scrofula

Mycobacterium tuberculosis

Patients report a painless, enlarging, or persistent mass. Systemic symptoms include fever/chills, weight loss, or malaise in 43% of patients.

Physical manifestations of M tuberculosis infection include the following:

- Any cervical node, although anterior cervical chain is more common
- Firm rubbery node becoming more firm and matted as disease progresses
- Infrequently, fluctuant with draining fistula
- Multiple masses in two thirds of patients
- Bilateral nodes in one third of patients

Nontuberculous mycobacterium

Patient history for nontuberculous mycobacterium includes the following:

- Chronic cervicofacial mass
- Clinical progression of the disease
- No constitutional symptoms
- Poor response to conventional antibiotics
- No history of tuberculosis exposure

A nontender slightly fluctuant mass is present with the overlying skin obtaining a violaceous hue. This is referred to as a cold abscess because of its lack of calor, or warmth. As the lesion progresses, the skin can become adherent to the underlying mass. This stage may progress to rupture and sinus formation.

Etiology of Scrofula

Cellular immunity, in particular the T-cell population, is instrumental in controlling infection. Activated T cells generate cytokines that enable tissue macrophages and monocytes to destroy the mycobacteria and form a tubercle or granuloma. Therefore, in the population with HIV, the incidence of tuberculous infection is 500 times greater than in the general population. Nontuberculous mycobacterium (NTM) generally occurs in immunocompetent hosts.

Differential Diagnosis of Scrofula

The differential diagnosis of scrofula includes the following:

- Cervicofacial lymphangiomas
- Congenital malformations of the neck
- Fine-needle aspiration of neck masses
- Lymphomas of the head and neck
- Malignant nasopharyngeal tumors
- Neck cancer of unknown primary site
- Neck cervical metastases
- Neck cysts
- Ranulas and plunging ranulas
- Salivary gland neoplasms
- Thyroid cancer

Other problems to be considered include congenital-developmental problems (eg, sebaceous cyst, branchial cleft cyst, thyroglossal duct cyst, lymphangioma/hemangioma, dermoid, laryngocele, pharyngeal diverticulum, thymic cyst); infectious complications (eg, bacterial, viral, cat-scratch, actinomycosis, fungal, atypical mycobacterium); and neoplastic complications (eg, metastatic, such as unknown primary, epidermoid carcinoma, melanoma, adenocarcinoma; primary, such as thyroid, lymphoma, salivary, lipoma, paraganglioma, rhabdomyosarcoma)

Laboratory Studies

No specific laboratory tests are recommended for scrofula; however, the workup for a neck mass may include cat-scratch titers, CBC count, and HIV testing.

Imaging Studies

CT scanning or MRI

Although both modalities can accurately depict sites, pattern, and extent of disease, they have limitations and findings are nonspecific.[5] Tuberculosis-infected nodes are frequently mistaken for metastatic carcinoma.

Chest radiography

For tuberculosis, despite the fact that cervical adenitis is usually secondary to a bronchopulmonary infection, review of the literature shows the rate of positive findings to be disappointingly low, averaging from 10 to 24% in patients with scrofula. For nontuberculous mycobacterium (NTM), findings are normal.

Ultrasonography

A study by Moon et al indicated that ultrasonography can be used to diagnose tuberculous lymph nodes of the neck in regions of the world where tuberculosis is endemic. The study involved 476 patients, including 69 with confirmed tuberculous lymph nodes and the rest with neck lymph nodes that were nontuberculous benign or malignant. With regard to the tuberculous nodes, the investigators reported that ultrasonography had a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 90.9%, 96.4%, 81.1%, 98.4%, and 95.6%, respectively.[6]

Other Tests and Procedures for Scrofula

Purified protein derivative

For tuberculosis, skin testing with partial purified protein derivative (PPD) has been fairly reliable. Generally, more than 85% of patients have a positive test of greater than 10 mm of induration. PPD should be the first line of investigation in the workup of a patient with a neck mass. Usefulness is diminished in individuals who have immunosuppression secondary to anergy.

For nontuberculous mycobacterium (NTM), response is variable. Known cross-reactivity to standard PPD exists, and induration typically is less than 10 mm. Skin-test antigens for various NTM are available from the Centers for Disease Control and Prevention (CDC) in Atlanta. However, they are not commonly used secondary to lack of standardization, difficulty in interpretation, and ubiquity of organisms.

Fine-needle aspiration

Fine-needle aspiration is a useful initial procedure with a sensitivity of 77% and specificity of 93%. The positive predictive value approaches 100%. The most reliable criteria for diagnosing infection are the presence of stainable acid-fast bacilli and cultured organisms on aspirate. Granuloma formation is highly suggestive but not definitive. Cultures take 4-6 weeks for growth; however, the newer polymerase chain reaction (PCR) techniques are promising.[7]

Regarding excisional or incisional biopsies, for tuberculosis, biopsies are potentially hazardous because they may spread the disease and give rise to sinus formation. For NTM, excisional biopsy has both diagnostic as well as therapeutic efficacy.

Histologic Findings for Scrofula

Mycobacterium tuberculosis is referred to as an acid-fast bacillus secondary to its resistance to destaining by acid-alcohol treatment. The Ziehl-Neelsen technique demonstrates an obligate aerobe, a nonmotile, slender, slightly beaded, and bent rod. The presence of caseating granulomas may be observed.

Definitive diagnosis of nontuberculous mycobacterium (NTM) is based on objective identification of the organism by culture. NTM is characterized by specific growth characteristics and the ability to form pigments on culture.[8]

Features claimed to be more representative of NTM lymphadenitis are the following:

- Ill-defined or nonpalisading granulomas
- An irregular or serpiginous character of the granuloma
- A nonspecific granulomatous response with ill-defined aggregates of epithelial lymphocytes
- Minimal or no caseous necrosis
- Few giant cells
- Variable-sized granulomas in different stages of evolution
- Basophilic nuclear debris in the center of necrotic granulomas.

However, the subjectivity of histopathologic interpretation of the above findings does not allow for conclusive diagnosis. Positive cultures are reported in most studies to be extremely difficult to obtain and are not necessary for diagnosis if other indicators are present, including age and presentation consistent with NTM, normal findings on chest radiograph, and weakly positive or negative PPD.

Treatment of Scrofula

Medical care

In general, *Mycobacterium tuberculosis* infection is not considered a localized disease; therefore, systemic chemotherapy should be instituted. Medical treatment alone is the standard treatment for scrofula. Antibiotic regimens effective for pulmonary infection can be applied to tuberculous lymphadenitis. Several options exist, including daily, twice-weekly, and thrice-weekly administration. The most common regimen consists of a 4-drug empiric treatment of isoniazid, rifampin, pyrazinamide, and ethambutol. After sensitivities return, continue 2 drugs for a total of 6 months.

Antituberculous therapy alone has substantial drawbacks in the treatment of nontuberculous mycobacterium (NTM) secondary to the lack of in vitro susceptibility. Reports of the clinical efficacy of clarithromycin in patients with AIDS and *Mycobacterium avium-intracellulare* (MAI) complex have prompted its use in NTM lymphadenitis. The use is primarily based on anecdotal evidence, and clinical efficacy in the literature is sparse. The low incidence of NTM lymphadenitis has precluded controlled trials.

Starke recommends chemotherapy when the family refuses surgery, a recurrence after surgery occurs, or the surgeon can excise only a particular amount of abnormal tissue.[9] The optimal treatment regimen is unknown.[10]

Luong and McClay showed that over 50% of nontuberculous mycobacteria can respond to medical therapy, often times with clarithromycin (Biaxin) alone.[11] If a 2-month trial of treatment shows no benefit, then surgical intervention should be considered.

Surgical care of M tuberculosis

Surgery alone has had disappointing results and is plagued by a high rate of recurrence and fistulizations. Surgery is reserved for establishing the diagnosis, advanced local disease, persistent disease, or draining fistula.

Failure to provide adequate chemotherapy at the time of surgery may lead to postoperative fistulas and hematogenous spread.

Surgical care of nontuberculous mycobacterium

Traditionally, surgical intervention ranging from simple aspiration to complete excision is the treatment of choice. Uniformly, simple incision and drainage is not recommended because of the high rate of fistulization and recurrence. Complete surgical excision is preferred; however, this procedure is not without risks, including injury to the facial nerve and scar formation with unacceptable cosmesis. If complete excision is attempted, removing all regional lymph nodes is not necessary because satellite nodes do not appear to be associated with recurrent disease.

In order to circumvent complete excision and risking injury to facial nerve or poor cosmesis, 2 alternatives are available. Alessi et al reported a series of 9 patients who underwent aspiration alone, all of whom had complete resolution.[8] Kennedy et al also described a series of 9 children who underwent curettage;[12] no complications occurred, all healed without scarring, and no recurrence was documented with a follow-up of 6-20 months.

In conclusion, complete excision of the offending nodes is the treatment of choice. However, when large areas of skin must be resected or the facial nerve is at risk, curettage or repeated needle aspiration serve as 2 efficacious alternatives.

Consultations

Consultations include the following:

- Primary care or infectious disease physician
- Health department contact for tuberculosis (TB)

Further outpatient care

Baseline tests prior to medical treatment include hepatic function, bilirubin, BUN/creatinine, and platelet count.

Clinically monitor patients once a month, and initiate laboratory monitoring if symptoms suggest toxicity. Some recommend liver function tests at least in the first and third months. Obtain uric acid levels for pyrazinamide toxicity, and assess visual acuity for ethambutol toxicity.

Complications

Complications associated with *Mycobacterium tuberculosis* include disseminated disease and chronic draining fistula. Complications associated with nontuberculous mycobacterium include scar formation.

A retrospective study by Chahed et al indicated that independent risk factors for a paradoxical reaction in cervical lymph node tuberculosis (TB) are lymph nodes swollen to at least 3 cm in size and associated extra-lymph node TB.[13]

Prognosis

Clinical remission rates for Mycobacterium tuberculosis approach 100% with medical treatment. For nontuberculous mycobacterium, clinical remission rates are greater than 95% with surgical treatment.

Patient Education

For patient education information, see the Bacterial and Viral Infections Center, as well as Tuberculosis.

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