Tuberculous Lymphadenitis

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Abstract

Lymphadenitis is the most common extrapulmonary manifestation of tuberculosis. It remains both diagnostic and therapeutic challenge because it mimics other pathologic processes and yields inconsistent physical and laboratory findings. Diagnosis is difficult often requiring biopsy. A thorough history and physical examination, staining for acid-fast bacilli, fine-needle aspiration and PCR are helpful in obtaining an early diagnosis. It is also important to differentiate tuberculous from nontuberculous mycobacterial cervical lymphadenitis because their treatment protocols vary. Treatment monitoring is more complex due to peculiar behavior of TB lymph nodes. Situation has become worse due to sharp increase in the incidence of atypical mycobacteria, poorly controlled HIV epidemic and rise of drug-resistant TB lymphadenitis. Tuberculous adenitis is best treated as a systemic disease with antituberculosis medication. Surgical therapy along with antituberculosis medication can be beneficial in selected patients.

History

Mycobacterial lymphadenitis has plagued humanity since long. The classic term scrofula derived from the Latin word glandular swelling. Hippocrates (460–377 B.C.) mentioned scrofulous tumours in his writing. The European kings of the Middle Ages imparted the royal touch to cure the “King’s evil” to which mycobacterial lymphadenitis referred.1 Albucasis in his Practica included surgical excision of the glands.2

Epidemiology

There are nearly 9 million new cases and 2 million deaths from tuberculosis world wide every year.3 The incidence of mycobacterial lymphadenitis has increased in parallel with the increase in the incidence of mycobacterial infection worldwide. TB lymphadenitis is seen in nearly 35 per cent of extrapulmonary TB which constituted about 15 to 20 per cent of all cases of TB. In HIV-positive patients, extrapulmonary TB account for up to 53 to 62 percent cases of TB.4-6 Cervical lymph nodes are the most common site of involvement and reported in 60% to 90% patients with or without involvement of other lymphoid tissue.7 Cervical lymphadenitis, which is also referred to as scrofula, may be manifestation of a systemic tuberculous disease or a unique clinical entity localized to neck. Mycobacterium tuberculosis is the most common causative agent in India.8-10 The incidence of mycobacterial lymphadenitis primarily depends on the endemicity of the of Mycobacterium tuberculosis. Lymphadenopathy due to non-tuberculous mycobacterial (NTM) is uncommonly reported from India.4 In nontuberculous adenitis, Mycobacterium avium-intracellulare complex is the most common causative agent. Mycobacterial lymphadenitis most frequently affects patients in their second decade but may afflict patients of any age. There is a female predominance (approximately 2:1) in most of the studies.11 Racial and ethnic minorities, foreign born, black and Asians are more likely than non-Hispanic white patients to develop tuberculous lymphadenitis. There is increased frequency of mycobacterial lymphadenitis in Asian population.11,12 Infection with the human immunodeficiency virus (HIV) is associated with an increased frequency of both pulmonary and extrapulmonary tuberculosis particularly lymphadenitis.13,14

Pathogenesis

Tuberculous lymphadenitis is a local manifestation of the systemic disease.12 It may occur during primary tuberculous infection or as a result of reactivation of dormant foci or direct extension from a contiguous focus. Primary infection occurs on initial exposure to tubercle bacilli. Inhaled droplet nuclei are small enough to pass muco-ciliary defences of bronchi and lodge in terminal alveoli of lungs. The bacilli multiply in the lung which is called Ghon focus. The lymphatics drain the bacilli to the hilar lymph nodes. The Ghon focus and related hilar lymphadenopathy form the primary complex. The infection may spread from primary focus to regional lymph nodes. From the regional nodes, organism may continue to spread via the lymphatic system to other nodes or may pass through the nodes to reach blood stream, from where it can spread to virtually all organ of the body. Hilar, mediastinal and paratracheal lymphnodes are the first site of spread of infection from the lung parenchyma. Supraclavicular lymph node involvement may reflect the lymphatic drainage routes for the lung parenchyma.15 Cervical tuberculous lymphadenitis may represent a spread from the primary focus of infection in the tonsils, adenoids sinonasal or osteomyelitis of the ethmoid bone.6,16 In untreated primary tuberculosis of children, enlargement of hilar and paratracheal lymph nodes (or both) become apparent on chest radiographs.

In initial stage of superficial lymph node involvement progressive multiplication of the M. tuberculosis occurs, the onset of delayed hypersensitivity is accompanied by marked hyperemia, swelling, necrosis and caseation of the centre of the nodes. This can be followed by inflammation, progressive swelling and matting with other nodes within a group. Adhesion to the adjacent skin may result in induration and purplish discolouration. The centre of the enlarging gland becomes soft and caseous material may rupture into surrounding tissue or through skin with sinus formation. Tuberculous mediastinal lymphadenitis may enlarge and cause compression of major blood vessels, phrenic or recurrent laryngeal nerves or cause compression of major blood vessels, phrenic or recurrent
Clinical Presentation

Lymphadenitis is the most common clinical presentation of extrapulmonary tuberculosis. Tuberculous lymphadenitis can be a local manifestation of the systemic disease. Tuberculous lymphadenitis most frequently involves the cervical lymph nodes (Figure 1) followed in frequency by mediastinal, axillary, mesenteric, hepatic portal, peripancreatic intestinal or hepatic lymph nodes. As immune deficiency advances HIV infected patients were atypical pulmonary diseases resembling primary or extra-pulmonary or disseminated tuberculosis. 

The lymphadenitis due to non-tuberculous mycobacteria is transmitted from environment by ingestion, inhalation, inoculation etc. The portal of entry for NTM may be the oral mucosa or gingiva. This is particularly important in children, because deciduous teeth may harbor the NTM that may reach the neck sites around the mandible through the lymphatics.

Diagnosis

A high index of suspicion is needed for the diagnosis of mycobacterial cervical lymphadenitis. A thorough history and physical examination, tuberculin test, staining for acid-fast bacilli, radiologic examination, and fine-needle aspiration cytology (FNAC) will help to arrive at an early diagnosis of mycobacterial lymphadenitis which will allow early institution of treatment before a final diagnosis can be made by biopsy and culture. The differential diagnosis is extensive and includes infections (viral, bacterial or fungal), and neoplasms (lymphoma or sarcoma, metastatic carcinoma), non-specific reactive hyperplasia, sarcoidosis, toxoplasmosis, cats-scratch fever, collagen vascular diseases and diseases of reticuloendothelial system.

Smears

Smears can be obtained either from a draining sinus or by FNA. Ziehl-Neelsen staining of the smears may reveal mycobacteria in the fresh specimens. Chance of finding AFB is higher in patients with cold abscess. The sensitivity and specificity of FNA cytology in the diagnosis of tuberculous lymphadenitis are 88% and 96%, respectively. Combination of FNA with culture or a Mantoux test further increases the diagnostic yield in mycobacterial cervical lymphadenitis. FNAC is a sensitive, specific and cost-effective way to diagnose mycobacterial cervical lymphadenitis, especially in children presenting with a suspicious neck swelling.
findings are inconclusive repeatedly, tissue biopsy by surgery is advisable.6,18,41,47

Culture

Culture of mycobacterium is diagnostic for mycobacterial cervical lymphadenitis. However, a negative culture result should not exclude the diagnosis of mycobacterial cervical lymphadenitis. The presence of 10–100 bacilli per cubic millimeter of the specimen is enough for a positive culture result. Different media can be used to culture the mycobacteria (L-J, Middlebrook, Bactec TB). However, several weeks are needed to obtain the culture result, which may prolong the initiation of treatment. Cultures are positive in 10–69% of the cases.20,48,49

Tuberculin Test

This intradermal test (Mantoux test) is used to show delayed-type hypersensitivity reactions against mycobacterial antigen, in which the reagent is mostly protein purified derivative (PPD). The test becomes positive 2–10 weeks after the mycobacterial infection. Positive reactions (>10-mm induration) can occur in M. tuberculosis infections. Intermediate reactions (5- to 9-mm induration) can occur after BCG vaccination, M. tuberculosis infection or nontuberculous mycobacterial infections. Negative reactions (< 4-mm induration) represent a lack of tuberculin sensitization. False-negative reactions can occur in about 20% of all persons with active tuberculosis. The test may be positive in different conditions, like other infections, metabolic disease, malnutrition, live virus vaccination, malignancy, immunosuppressive drugs, newborns, elderly people, stress, sarcoidosis and inadequate test application.

The tuberculin test is considered diagnostic in mycobacterial infections, though its value in diagnosing disease is debated.42,50 Children with atypical mycobacterial adenitis have a decreasing tuberculin response to repeated testing, while children with tuberculous adenitis have a stable response.51 In mycobacterial cervical lymphadenitis cases the test may be positive (49.4%), intermediate (35.6%) or negative (15%).20

Molecular Testing

Polymerase chain reaction (PCR) is a fast and useful technique for the demonstration of mycobacterial DNA fragments in patients with clinically suspected mycobacterial lymphadenitis.52,53 The presence of few dead or live microorganisms is enough for PCR positivity. The PCR can be applied on the materials obtained by FNA or biopsy, and can reduce the necessity for open biopsy.54,55 Its sensitivity ranges between 43 and 84%, and its specificity between 75 and 100%.52,56 PCR can be applied when smears and cultures are negative.57 PCR is a confirmatory and sensitive technique for the diagnosis of mycobacterial cervical lymphadenitis. It can differentiate between lymphadenitis caused by Mycobacterium tuberculosis and that caused by NTM. PCR is used as an adjunct to conventional techniques in the diagnosis of mycobacterial infections.55,56 The PCR should only be reserved for problem cases in resource limited countries.

Histopathology

Histopathologic examination is diagnostic of mycobacterial cervical lymphadenitis.58,59 Langerhans giant cells, caseating necrosis, granulomatous inflammation and calcification can be seen.60 The presence of microabscesses, ill-defined granulomas, noncaseating granulomas and a small number of giant cells is more prominent in nontuberculous adenitis when compared with tuberculous adenitis.60,61 Radiology and imaging

Chest radiograph, ultrasound, CT and MRI of the neck can be performed in mycobacterial lymphadenitis. Associated chest lesions as seen on chest radiography are very common in children but less common in adults, evident nearly 15% cases.6,16,21 Ultrasound of the neck can demonstrate singular or multiple hypoechoic and multiloculated cystic lesions that are surrounded with thick capsule.

On CT, the presence of conglomerated nodal masses with central luscency, a thick irregular rim of contrast enhancement and inner nodularity, a varying degree of homogeneous enhancement in smaller nodes, dermal and subcutaneous manifestations of inflammation, such as thickening of the overlying skin, engorgement of the lymphatics and thickening of the adjacent muscles, and a diffusely effaced fascial plane may suggest mycobacterial cervical lymphadenitis.62,63 However, these findings may also be seen in other diseases like lymphoma and metastatic lymphadenopathy.62 MRI may reveal discrete, matted and confluent masses. Necrotic foci, when present, are more frequently peripheral rather than central, and this together with the soft tissue edema may be of value in differentiating mycobacterial cervical lymphadenitis from metastatic nodes.64 If the cervical mass is necrotic, there will be low and high signal intensity in the center of the mass in T1- and T2-weighted images, respectively.

Treatment

Antituberculosis treatment is the mainstay in the management of TB lymphadenitis. The National Tuberculosis Programmes worldwide follow the World Health Organization’s guidelines, directly observed treatment, short-course (DOTS) approach as intermittent chemotherapy for patients with TB lymphadenitis. According to the DOTS guidelines TB lymphadenitis is categorised under treatment category III.65 Those with smear positive TB lymphadenitis with pulmonary involvement or severely ill are categorised under treatment category I. While the six months treatment may be sufficient for many patients, each patient has to be individually assessed and, where relevant, treatment duration may have to be extended.4 It is difficult to define a clear cut ‘end point’ for assessing the efficacy of treatment of such extrapulmonary tuberculosis with delayed response to treatment and limited controlled clinical trials.66 Recent randomized controlled trial on 268 patients at Tuberculosis Research Centre (TRC, Chennai) showed that both the self-administered daily regimen and the fully observed twice-weekly regimen are highly efficacious for treating patients with lymph node tuberculosis.67 Earlier studies in India also have shown that children can be successfully treated with a short course chemotheraphy regimen of six months.10 A tuberculous infection usually responds very well to antituberculous chemotherapy, whereas a nontuberculous mycobacterial infection usually require a surgical intervention.68 The long-term efficacy of short-course treatment regimens of TB lymphadenitis and other extra-pulmonary tuberculosis has been well documented in another Indian study.69 The ATS/CDC/IDSA Committee (2003) indicated that therapeutic lymphnode excision is not indicated except in unusual circumstances.65 There are two groups of antituberculosis drugs. First-line drugs are isoniazid (INH), rifampin, ethambutol, pyrazinamide and streptomycin. Second-line drugs, which are less efficacious and more toxic than the first-line drugs, are capreomycin, kanamycin, ethionamide, thiacetazone, para-
aminosalicylic acid and cycloserine. Treatment should not be deferred during pregnancy.65 Lymph nodes can enlarge with worsening symptoms in the course of tuberculosis treatment which are called “paradoxical reactions”. Generally, no modification or prolongation in antituberculosis treatment regimen is indicated.10 In few cases even after treatment FNAC may remain positive for tuberculosis and even for AFB because of dead bacilli. Therefore treatment in such cases should be given in culture-positive cases only.

Surgery

Lymph node excision usually is not indicated. In nontuberculous adenitis and some selected cases, surgery is more useful: it provides a rapid tissue diagnosis and confirms the bacterial type.30,76,77 Surgery increases the cure rate with excellent cosmetic result and a low complication rate.72 Antibiotics are used to augment surgical therapy.72 Surgical techniques include aspiration, incision and drainage, curettage, complete surgical excision of the affected lymph nodes and the overlying skin and selective nodal or functional neck dissection when required. When lymph nodes are fluctuant and ready to drain, antigravity aspiration should be done. Complete surgical excision of all affected tissue can be done when feasible.26 Aspiration, which may result in 50% cure rate, can be performed when surgical excision is limited. Curettage, which may result in 70% cure rate, can also be made when the lesion is in proximity to the nerve or there is extensive skin necrosis.44 Simple incision and drainage are associated with prolonged postoperative wound discharge and hypertrophic scarring.72 Excision of the skin overlying the mass can be performed when there is a fistula, scar formation, or necrosis.

Corticosteroids

The usefulness of corticosteroids in the treatment is not well established and controversial.14 HIV infection and antiretroviral drugs

The treatment of mycobacterial lymphadenitis in HIV infected patients is same as in those without HIV infection. The rifampicin decreases the serum concentrations of antiretroviral agents to subtherapeutic levels. In those cases rifapentine can be used instead of rifampicin along with INH in continuation phase.65,76,77 The CD4+ and CD8+ T lymphocyte counts must be estimated and highly active antiretroviral treatment (HAART) must be administered when indicated.

During antituberculosis therapy, affected nodes may enlarge or new nodes may appear, representing an immune response to killed mycobacteria. Patients with TB lymphadenitis especially those who are co-infected with HIV may develop paradoxical reactions while on antitubercular drugs. A similar phenomenon is also seen in patients with HIV infection who begin concurrent antiretroviral therapy is a result of immune reconstitution. Paradoxical response to treatment with further enlargement or additional swelling of new lymph nodes may occur in 6-30% of patients within the first two months of antitubercular treatment.22,71

With treatment reduction of size of the lymph nodes swelling without complications may occur in 70-90% of patients.22,71 Early institution of specific antituberculosis treatment and close clinical monitoring for adverse drug reactions are the key to the successful management.65,76

Conclusion

Tuberculosis is a systemic disease and lymphadenitis is the most common extrapulmonary manifestation of the disease. Their diagnosis and distinction need a high index of suspicion, and application of a variety of diagnostic modalities. The approach to diagnosis should be individualized depending on the location of the disease and the clinical evaluation. Tuberculous adenitis is best treated with antituberculosis medication and in addition surgical treatment is more useful in selected cases.

References


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**Announcement**

**5th East Zone Rheumatology Conference and 3rd Biannual Conference**

The 5th East Zone Rheumatology Conference and 3rd Biannual Conference, IRA- Assam chapter will be held at Guwahati on 12th & 13th September, 2009. It will be organized by Indian Rheumatology Association, Assam Chapter.

For details contact: Organizing Secretary, Dr. Pradip Kumar Sarma, MD (Medicine), DM (Clinical Immunology), Guwahati, Assam, Mobile: 9707023625

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**Announcement**

**ISECON 2010**

Indian Society of Electrocardiology is organizing its Annual Conference - ISECON 2010 on 19th - 21st February, 2010 at Hotel Renaissance, Mumbai

For further details please contact: Dr. S.B. Gupta, Hon. Secretary, ISE, Head, Department of Medicine and Cardiology, Central Railway Headquarters Hospital, Byculla, Mumbai 400 027. Tel.: 23732911 (Hospital), 22624556 (Residence), 22651044 (Fax) • Mobile: 09821364565 / 09987645403 • e-mail: sbgupta@vsnl.net • website: www.iseindia.org