Review

Tuberculosis Lymphadenitis in Ethiopia

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SUMMARY: Tuberculosis (TB) is one of the most serious public health challenges in Ethiopia. Indeed, Ethiopia ranks 7th among 22 countries with a high burden of TB worldwide. Both pulmonary TB and extrapulmonary TB (EPTB) are issues of concern. Ethiopia ranks 3rd in terms of the number of EPTB patients worldwide, with TB lymphadenitis (TBL) being the most common. According to the World Health Organization’s Global TB Report 2009, the estimated number of TB patients in Ethiopia was 314,267 in 2007, with an estimated incidence rate of 378 patients per 100,000 population. Furthermore, 36% patients suffered from EPTB, with TBL accounting for 80% of these patients. In Ethiopia, pathological services, culture, and drug susceptibility testing for mycobacterium species are not available as routine tests, not even for cases with suspected infection by drug-resistant strains. Therefore, the management of multidrug-resistant (MDR) TB in Ethiopia is currently unsatisfactory. Against this background, a high index of clinical doubt and timely use of diagnostic methods, prompt confirmation of diagnosis, and early initiation of specific anti-TB treatment are the key factors for the successful management of MDR-TB and TBL in Ethiopia.

1. Introduction

Tuberculosis (TB) is one of the most serious public health challenges in Ethiopia. According to the World Health Organization (WHO) report in 2009 (1), Ethiopia ranked 7th among the 22 countries identified to have a high TB burden. Of these, 9 countries in Sub-Saharan Africa (Nigeria, Ethiopia, South Africa, Tanzania, Kenya, Congo, Uganda, Mozambique, and Zimbabwe) account for 1.5 million patients, with the incidence rates ranging between 305 and 525 per 100,000 population (2,3). The WHO’s Global TB Report 2009 indicated that the estimated number of TB patients in Ethiopia was 314,267 in 2007, with an estimated incidence rate of 378 patients per 100,000 population (Fig. 1). Furthermore, 36% patients suffered from extrapulmonary TB (EPTB), with TB lymphadenitis (TBL) accounting for 80% of these patients (4). The prevalence of and mortality from all forms of TB are estimated to be 546 and 73 per 100,000 population, respectively (5).

All types of TB ranked 4th among the leading causes

![Fig. 1. Incidence of TB in Ethiopia (per 100,000 population). Source: Global Tuberculosis Control Report, World Health Organization. Definition: Incidence of tuberculosis is the estimated number of new pulmonary, smear positive, and extrapulmonary tuberculosis cases.](image-url)
of hospital admission and 2nd among the causes of hospital death worldwide (2). After primary infection, TB can involve any organ system in the body. While pulmonary TB (PTB) is the most common presentation, EPTB is also an important clinical concern (6). The term EPTB has been used to describe isolated occurrences of TB at body sites other than the lungs. However, when an extrapulmonary focus is evident in a patient with PTB, the patient is diagnosed with PTB as per the WHO guidelines (7). The current prevalence of EPTB and its impact have not been clearly investigated in Ethiopia for various reasons, including the lack of expertise in diagnosing TBL, the lack of healthcare institutions, and the lack of reliable data, particularly from rural areas. Although TB bacteria can spread to any tissue, the organs commonly affected by EPTB include the lymph nodes, pleura, bones and joints, brain and meninges, gastrointestinal organs, liver, genitourinary organs, peritoneum, and pericardium. The purpose of this study was to review the status and impact of TBL in Ethiopia.

2. Epidemiology

The proportion of EPTB patients among all TB patients varies among countries. In a study that was conducted in the United States, 538 (28.6%) of 1,878 TB patients were diagnosed with EPTB. Women and immigrants were most commonly affected (8), and the lymph nodes were the most common sites of infection (43%) (9). Another study of TB conducted in Iran showed that the cervical lymph nodes were the most frequently involved sites; more than 50% of patients showed cervical lymph node involvement (10). A report from Germany indicated that 7–8% of all TB patients suffered from TBL (11), while a study from Spain indicated this figure to be 39% (25/65) (12). A retrospective study conducted in Taiwan evaluated 118 adult patients with AIDS and showed that 25% of these patients suffered from TB. Among the TB patients, 22 (76%) suffered from EPTB, with the most common site of infection being the lymph nodes (73%) (13).

In a study conducted in developing countries, where the incidence of TB is high, TBL was found to account for 30–64% patients with lymphadenopathy and 80% patients with EPTB (14). A study of lymph node biopsies conducted in Lusaka, Zambia revealed an increased TBL burden in central Africa (15). Even though the prevalence of TBL is increasing, only a few systematic studies have been conducted in Sub-Saharan Africa till date.

A few studies and hospital reports indicate that TBL accounts for a significant proportion of EPTB patients in Ethiopia. Immunocompromised individuals, especially HIV patients, are at an increased risk of EPTB, which accounts for more than 50% TB patients among all HIV-positive patients (16). According to the WHO report (17), Ethiopia is ranked 3rd, after India and South Africa but before China, in terms of the number of EPTB patients worldwide, most of whom are diagnosed with TBL (18). The incidence of EPTB among patients with newly diagnosed TB has been increasing over the years in Ethiopia, with a vast majority of patients being diagnosed with TBL. Reports from some regions of the country, such as the Tigray and Amhara regions, indicate that TBL is estimated to account for 39% of all TB patients (19). The results of the evaluation by the Annual Joint Review Mission of TB and Leprosy Control Programme (TLCP) of Ethiopia also noted that, in a number of treatment units, more than half of all newly registered TB patients were found to suffer from EPTB (Table 1).

According to previous findings on TB, one would expect that 15 of every 100 new TB patients would suffer from EPTB, thus accounting for 30–40% of all TB patients (20). The situation in Ethiopia seems to be consistent with the epidemiological findings reported above. In 2006/2007, the proportion of EPTB patients was 36.6% in Ethiopia (21), as opposed to the proportion in high-burden Asian countries such as India (14.9%), China (4%), and Indonesia (2.5%) and other high-burden African countries such as South Africa (17.5%), Nigeria (4.3%), and Kenya (16.6%) (18). According to the case records obtained over a 7-year period (2001–2007) by the Afar Regional Health Bureau, approximately 28% TB patients suffered from EPTB, the most common form being TBL (17). Other studies performed in different parts of the country also indicated an increased proportion of TBL patients. According to a study conducted in Butajira (rural Ethiopia), 40 (56%) of 72 patients with a clinical diagnosis of EPTB were confirmed to suffer from TBL (22). Of the 40 patients, 11 showed seropositivity for HIV. High mortality rates have been observed among HIV

<table>
<thead>
<tr>
<th>Year</th>
<th>PTB Smear-positive (%)</th>
<th>Smear-negative (%)</th>
<th>EPTB Smear-positive (%)</th>
<th>EPTB Total new cases</th>
<th>Treatment success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000/01</td>
<td>32,423 (36)</td>
<td>28,994 (32)</td>
<td>29,312 (32)</td>
<td>90,729</td>
<td>—</td>
</tr>
<tr>
<td>2001/02</td>
<td>35,915 (34)</td>
<td>32,197 (31)</td>
<td>37,138 (35)</td>
<td>105,250</td>
<td>—</td>
</tr>
<tr>
<td>2002/03</td>
<td>37,014 (34)</td>
<td>32,656 (30)</td>
<td>38,818 (36)</td>
<td>108,488</td>
<td>—</td>
</tr>
<tr>
<td>2003/04</td>
<td>41,430 (34)</td>
<td>37,119 (31)</td>
<td>42,477 (35)</td>
<td>121,026</td>
<td>—</td>
</tr>
<tr>
<td>2004/05</td>
<td>41,800 (31)</td>
<td>40,269 (33)</td>
<td>44,021 (36)</td>
<td>123,090</td>
<td>81%</td>
</tr>
<tr>
<td>2005/06</td>
<td>36,674 (31)</td>
<td>40,234 (33)</td>
<td>43,255 (36)</td>
<td>120,163</td>
<td>78%</td>
</tr>
<tr>
<td>2006/07</td>
<td>38,040 (30)</td>
<td>43,500 (34)</td>
<td>45,269 (37)</td>
<td>126,809</td>
<td>85%</td>
</tr>
</tbody>
</table>

patients coinfected with TB in Ethiopia. Another study conducted in the same region also showed that 107 (73%) of 147 patients were confirmed to suffer from TBL (23). Again, 24 of these 107 TBL-patients showed seropositivity for HIV. Moreover, a study from the Tikur Anbessa hospital showed that TBL accounted for 194 (95%) of 205 patients clinically diagnosed with lymphadenitis (24). A study of 128 patients with TBL undertaken at the Jimma University showed that the cervical lymph nodes were the most commonly affected (74%), followed by the axillary (20%) and inguinal lymph nodes (4%) (25). Furthermore, other studies conducted in different regions of the country reported a high proportion of TBL patients, ranging from 40–78% (26–32) (Fig. 2). This is in contrast to the national estimate of the proportion of EPTB patients (34%) (33). This difference may be due to the underestimation of EPTB incidence in most rural health centers in Ethiopia, which lack expertise and laboratory facilities. Differences in study design, including sample size, study subjects, geographical differences, and hospital set-up, and the policy of infection prevention and control may be other reasons for the disparity in study results among different regions.

According to a 2003/2004 report by the Ministry of Health TLCP, 41,430 (34%) patients with smear-positive PTB and 42,477 (35%) patients with newly diagnosed EPTB were documented (Table 1). During the 2001 External Evaluation and the 2002 Joint Review of the TLCP of Ethiopia, it was observed that in a number of treatment units, greater than 50% of all new cases registered were found to be EPTB cases, again with the vast majority being diagnosed as TBL (34). Delayed diagnosis of PTB, incomplete treatment of TB, HIV coinfection, and other underlying diseases may increase the prevalence of TBL in Ethiopia.

3. Etiological agents

The genus Mycobacterium includes members of the Mycobacterium tuberculosis complex, such as M. tuberculosis, M. bovis, M. africanum, M. microti, and M. canettii (35). M. tuberculosis, M. bovis, M. africanum, and the so-called atypical mycobacteria (mycobacteria other than TB [MOTT]) can cause lymphadenitis. However, lymphadenitis caused by the M. tuberculosis complex seems to adopt a more chronic course compared with lymphadenitis caused by MOTT, which result in a more rapid clinical course (12). In developed countries, MOTT are the most common causes of TBL (36). A report on mycobacterial lymphadenitis from the United States showed that while 95–98% adult patients were infected by M. tuberculosis, 86–92% children were infected by MOTT (M. scrofulaceum, M. avium-intracellulare, and M. kansasi) (14). A study conducted with 1,817 TBL patients in southeast England showed that 1,677 (92.3%) patients were culture-positive for M. tuberculosis, 25 (1.34%) for M. bovis, 21 (1.16%) for M. africanum, and 94 (5.17%) for other environmental mycobacteria (37).

A study conducted in Sudan reported that M. tuberculosis was the causative agent of TBL in 96% patients (38). Information from Africa on TBL caused by M. bovis is scarce. In Tanzania, M. bovis was isolated from 4 of 17 biopsies obtained from patients with clinically suspected TBL (39), and recent reports from other African countries indicate the transmission of M. bovis to cause clinical disease in humans (40). Studies conducted in Ethiopia reported M. tuberculosis and M. bovis as the causative agents of TBL (22,23). In another study, 73.8% and 16.7% of 42 isolates were identified as M. tuberculosis and M. bovis, respectively (41). Another study conducted in southeast Ethiopia reported that 29 (82.9%) of 35 PCR-positive TBL patients were infected by M. tuberculosis while 6 (17.1%) were infected by M. bovis (22). Fetene et al. reported in 2011 (42) phenotypic method-based detection of M. bovis in 14.9% patients, while Beyene et al. reported in 2008 (32) M. tuberculosis to be a major cause of TBL. However, M. bovis appears to be a rare etiological agent of TBL in Ethiopia. However, these results should be interpreted with caution in countries like Ethiopia, where there are limited laboratory facilities for the diagnosis of mycobacterium species.

4. Pathogenesis

EPTB involvement can occur in isolation or along with a pulmonary focus, as in the case of patients with disseminated TB. M. tuberculosis most often gains entry into the body via the respiratory tract (43). The organism is transported to the hilar lymph nodes and proliferates (40) and disseminates into the hematicogenous and lymphatic systems. TBL is considered to be the local manifestation of a systemic disease, whereas MOTT lymphadenitis is thought to be a truly localized disease (43). During initial infection, regional, hilar, and mediastinal lymph nodes are always seeded with bacilli; other lymph nodes may also be involved (44). Sometimes, the tonsils are an important portal of entry. The infection then spreads via the lymphatic system to the draining cervical lymph nodes. Initially, the nodes may show a discrete periadenitis, resulting in matting and fixation of the lymph nodes. The lymph nodes subsequently coalesce and break down because of the formation of caseous pus (43). This may perforate the deep fascia and present as a collar-stud abscess (9). The overlying skin becomes indurated and breaks down as indicated in Fig. 3, resulting in sinus formation that may remain unhealed for years. Healing may occur at each of the stages, with calcification and scarring (45). In
contrast, MOTT gains entry into the lymph nodes directly via the oropharyngeal mucosa, salivary glands, tonsils, gingiva, or conjunctiva (46), and lymph node involvement represents a localized disease. Immune response develops 4 to 6 weeks after inhalation. Activated T cells recruit monocytes and mononuclear cells to the lung and lymph nodes, ultimately leading to granulomatous inflammation with giant cells, epithelioid cells, and lymphocytes. In most patients, the primary infection resolves without becoming clinically apparent and healing occurs by fibrosis and/or calcification.

5. Clinical manifestations

The clinical manifestations of TBL depend on the site of the lymphadenopathy and the immune status of the patient. It often affects children and young adults (47), with a predilection for females (10). Symptoms such as chest pain, dyspnea, fever, night sweating, anorexia, and hemoptysis are common among TB patients. In patients with TBL and HIV infection, there may be a substantial mycobacterial load with systemic clinical findings such as fever, weight loss, fatigue, cough, and night sweating (48). However, the most common presentation is isolated chronic lymphadenopathy in young adults without systemic symptoms. The mass may be present for up to 12 months before diagnosis (49). Patients usually present with gradual enlargement of the lymph nodes and may otherwise be asymptomatic (43). Physical examination reveals painless enlarged lymph nodes, often of varying size, a firm discrete mass, or matted nodes fixed to surrounding structures. The overlying skin may be indurated (49). The lymph nodes are not tender unless secondary bacterial infection is present. Cervical lymph nodes are more often affected than axillary, inguinal, mesenteric, mediastinal, and intramammary lymph nodes (48).

6. Transmission and risk factors

*M. tuberculosis* is transmitted through the airborne route, and there are no known animal reservoirs (44). Droplet nuclei are produced when patients with pulmonary or laryngeal TB cough, sneeze, speak, or sing. Not all patients with TB of the respiratory tract are equally efficient in transmitting the bacteria. Patients whose sputum smears are positive for acid-fast bacilli (AFB) have 5,000 or more organisms per milliliter of sputum (50) and infect many of their close contacts, whereas those who are smear-negative and culture-positive infect far fewer contacts. *M. tuberculosis* infection of the cervical lymph nodes also results by way of airborne droplets from or contact with infected humans. Organisms such as *M. bovis*, which are ingested with contaminated meat or unpasteurized milk, may cause EPTB, particularly, in the form of cervical lymphadenitis. MOTT usually enters the lymph nodes via the oral mucosa, salivary glands, and tonsils (43).

Individuals with prolonged or intense contact with infected individuals are at high risk of infection. Others at risk include residents and employees of high congregate settings, individuals living in endemic TB regions, and healthcare workers who serve high-risk clients. Well-recognized factors that lead to an increased risk of latent TB reactivation at an individual level include defects in cellular immunity, such as HIV infection, immunosuppression from solid organs and hematological malignancy or from the treatment of these conditions, and immunosuppressive drugs (51). Other factors that fuel TB infection and reactivation include poverty, diabetes mellitus, and smoking. A better knowledge of factors that lead to *M. tuberculosis* infection or increase the risk of active TB development is important for TB control.

7. Diagnosis

TBL may be difficult to diagnose. In most cases, the disease is suspected clinically. Its diagnosis by pathologist/microbiologists depends on histological assessment of granulomatous lesions and the detection of AFB. However, problems may occur when the disease is unsuspected. Therefore, histology should always include the detection of AFB using Ziehl-Neelsen (ZN) or fluorescence staining (52). However, the sensitivity of these methods is rather low (53) because the results based on AFB staining are negative in approximately 40% patients with culture-positivity. Individuals with prolonged or intense contact with infected humans are at high risk of infection. Others at risk include residents and employees of high congregate settings, individuals living in endemic TB regions, and healthcare workers who serve high-risk clients. Well-recognized factors that lead to an increased risk of latent TB reactivation at an individual level include defects in cellular immunity, such as HIV infection, immunosuppression from solid organs and hematological malignancy or from the treatment of these conditions, and immunosuppressive drugs (51). Other factors that fuel TB infection and reactivation include poverty, diabetes mellitus, and smoking. A better knowledge of factors that lead to *M. tuberculosis* infection or increase the risk of active TB development is important for TB control.

8. Treatment, prevention, and control

TBL is principally a medical disease. Anti-TB treatment is extremely important for the management of...
multidrug-resistant (MDR) TB and TBL. The WHO recommends a directly observed treatment that is a short-course (DOTS) approach for patients with TBL (3). The purpose of effective treatment is to cure the patient, interrupt transmission to other individuals, and prevent the development of drug-resistant strains. These goals are not achieved in many regions of the country, although anti-TB drugs are available. This may be attributed to patient non-adherence to treatment, clinician non-adherence to the national treatment guidelines, or both. In general, chemotherapy regimens that are effective for PTB should also be effective for TBL in Ethiopia. TB is treated with first-line drugs, including isoniazid, rifampicin, streptomycin, ethambutol, and pyrazinamide, in Ethiopia. In order to avoid the development of drug resistance, the drugs are prescribed in combinations of two or more (43). In countries with a high TB burden, such as Ethiopia, special emphasis needs to be placed on the treatment of new TB cases. This must include drug susceptibility testing, which is capable of identifying resistant strains.

Management of MDR-TB in Ethiopia is currently unsatisfactory (Table 3). MDR-TB is defined as TB resistant to the most effective first-line drugs, namely isoniazid and rifampin (54). TB caused by other types of resistant strains is termed extensively drug-resistant TB (XDR-TB). These strains are resistant to isoniazid, rifampin, and the second-line drugs used to treat MDR-TB. Multiple factors contribute to drug resistance in patients with M. tuberculosis infection, including incomplete and inadequate treatment or adherence to treatment, logistical issues, multidrug transporters, host genetic factors, and HIV infection. According to the WHO report in 2008, the prevalence of MDR-TB is 1.6% in newly diagnosed patients, and it is reportedly higher in patients who have previously received anti-TB treatment (11.8%). MDR-TB and XDR-TB are becoming increasingly important. Genotype studies have shown that 63–75% patients with XDR-TB progress through acquisition of resistance (55).

In conclusion, smear microscopy is insufficient for an accurate diagnosis. Culture of fine-needle aspiration, biopsy specimens, or other specimens as well as molecular techniques are important for diagnosis. TB control must be improved in Ethiopia to achieve the effective cure rate targeted by the WHO. Therapeutic guidelines, in particular the length of treatment and bacteriological follow-up, should be adequately implemented in Ethiopian hospitals. DOTS or similar strategies should be evaluated to decrease the number of patients who interrupt therapy or become lost to follow-up. Therefore, a high index of clinical doubt and timely use of diagnostic methods, prompt confirmation of diagnosis, and early initiation of specific anti-TB treatment are the key factors for the successful management of MDR TB and TBL in Ethiopia.

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Conflict of interest None to declare.

REFERENCES


