Lymph node tuberculosis in patients from regions with varying burdens of tuberculosis and human immunodeficiency virus (HIV) infection

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Résumé

Tuberculose ganglionnaire chez des patients originaires de pays de prévalences de tuberculose et d’infection par le virus de l’immunodéficience humaine (VIH) variables

Objectifs > Les études de cohortes de tuberculose ganglionnaire dans les pays développés portent généralement sur de petits effectifs. Nous décrivons une cohorte d’adultes originaires de trois zones géographiques avec des prévalences de tuberculose-maladie et d’infection à virus de l’immunodéficience humaine (VIH) très différentes.

Méthodes > Étude monocentrique rétrospective décrivant tous les patients ayant une tuberculose ganglionnaire prouvée bactériologiquement entre mars 1996 et avril 2005.

Résultats/Discussion > Quatre-vingt-douze patients ont été étudiés. Les malades positifs pour le VIH avaient un risque significativement plus élevé de tuberculose disséminée, de signes généraux, et donc d’hospitalisation. L’abord ganglionnaire, que ce soit par ponction à l’aiguille fine ou par biopsie-exérèse, avait une rentabilité élevée et assez proche l’une de l’autre à la culture. La

Summary

Background > Few large cohorts of patients with lymph node tuberculosis (LNTB) have been reported in developed countries.

Objective > To describe the epidemiological and clinical characteristics of LNTB in patients living in France but born and raised in geographic areas with varying burdens of tuberculosis and human immunodeficiency virus (HIV) infection.

Design > A retrospective study of all patients with bacteriologically-proven LNTB assessed in a French hospital from March 1996 through April 2005.

Results > The analysis included 92 patients. HIV coinfected patients had a higher risk than those without HIV of presenting with disseminated TB and systemic symptoms and of hospitalization. Lymph node diagnostic procedures had a high yield when samples were cultured. About 25% of patients had an abnormal chest radiograph, and most of them were positive for acid-fast bacilli on sputum smears or for Mycobacterium tuberculosis culture. Treatment was generally prescribed for a longer duration than that recommended by international guidelines. One quarter of the patients developed a paradoxical reaction. A high proportion of
Lymph node tuberculosis (LNTB), also known as tuberculous lymphadenitis, is the most common form of extrapulmonary TB [1]. Its epidemiology and diagnostic aspects vary according to the patient’s geographic origin and the burden of TB and human immunodeficiency virus (HIV) infection in the country of origin [2]. In sub-Saharan African countries, with generalized HIV epidemics and high TB incidence, all types of active TB have increased tremendously in the last 15 years [3]. TB is the most frequent opportunistic infection in HIV-infected patients, and more than 25% of TB patients are coinfected with HIV [4]. HIV-infected patients often present with unusual clinical manifestations, particularly extrapulmonary or disseminated TB [5]. In India, extrapulmonary TB accounts for approximately 20% of all TB cases, and the lymph nodes are the most frequent extrapulmonary site. Extrapulmonary TB classically occurs in young women without HIV infection [6]. In most Asian countries where the HIV rate is low or concentrated but the incidence of TB is high, HIV coinfection is present in about 5% of newly diagnosed adult TB cases [7].

The incidence of TB and prevalence of HIV infection are both low among native Western European populations. In a cohort of native-French HIV-infected patients, TB was the least common opportunistic infection [8]. TB and HIV infection rates in Europe are associated with the migratory flow of people from high-burden countries. In France, for example, TB incidence is 5/100,000 native French people, compared to 160/100,000 for those born in Africa [9]. In 2006, natives of sub-Saharan Africa accounted for 18% of new TB [9] cases and 27% of newly diagnosed HIV infections in France [10]; corresponding figures for those born in Asia are 7% and 1% and for those from North Africa, a setting with intermediate TB incidence and low HIV prevalence, 13% and less than 2%, respectively [9,10].

The individual genetic characteristics and the bacterial genotype of M. tuberculosis (MTB) are important factors in determining the risk of developing active TB, the specific type of TB, and its dissemination throughout or location within the body [11]. TB is often due to reactivation of latent infection, so that emigrants who develop active TB in the country they are living in often do so with the MTB strain circulating in their country of origin [12]. Environmental factors, i.e., intensity of exposure to MTB associated with socioeconomic conditions, and underlying factors, i.e., diseases affecting the immune response, in

What was known

- Coinfection with tuberculosis (TB) and human immunodeficiency virus (HIV) is common.
- Default rates for TB treatment are high in areas where directly observed therapy, short course (DOTS), is not applied.
- Most of the TB cases diagnosed in France originate from high-burden countries.

What this study adds

- Disseminated TB is frequent even in patients without HIV infection.
- It is important to perform bacteriologic cultures of lymph node aspirate and biopsy samples from all clinically involved sites.
- Consideration of the patient’s country of origin can help in the differential diagnosis of lymph node pathologies.
particular HIV infection, are additional drivers of tuberculosis epidemiology at a public health level [13]. The country of origin acts as a crude proxy for the estimated risk of presenting with active TB, after taking into account the interactions between ethnicity-related host susceptibility, the virulence of circulating MTB strains, the underlying socioeconomic conditions, and the prevalence of associated diseases, especially HIV, in that particular area. A patient’s country of origin can thus help in the differential diagnosis of lymph node diseases, based on their respective frequencies among native inhabitants of specific countries [2,14].

This retrospective study compared the epidemiological characteristics, clinical features, laboratory findings, diagnostic test yields, treatment and outcome of bacteriologically-proven LNTB in France among natives of regions with differing burdens of TB and HIV infection. We also compared these features in TB patients with and without HIV coinfection.

Methods

Patients

The study collected and retrospectively reviewed the medical records of all adults with a bacteriologically-proven diagnosis of LNTB seen at the Internal Medicine Department of the Hospital Lariboisière (as either inpatients or outpatients), Paris, France, from March 1996 through April 2005. We collected demographic characteristics, clinical presentations, imaging findings, diagnostic procedures, microbiology and other laboratory results, TB treatments, and outcomes. Patients were pooled into groups stratified by the incidence of TB and prevalence of HIV infection in their native country, according to the World Health Organization (WHO). Patients were considered to be natives of a particular country if they were born there and had spent most of their childhood there.

Countries were then classified into one of three groups:

- group A: low or intermediate TB incidence, low HIV prevalence (Western Europe/North Africa);
- group B: high TB incidence, low HIV prevalence (India/Pakistan);
- group C: high TB incidence and high HIV prevalence (sub-Saharan Africa).

Ethical approval was not required for the study as it was a retrospective file review. Patient confidentiality was ensured.

Definition

The study included all patients with bacteriologically-proven LNTB in any peripheral or visceral lymph node, defined by the identification of MTB in a lymph node or, if lymph nodes enlarged at diagnosis had disappeared during TB treatment, at any another site. We defined localized LNTB as one or more enlarged lymph nodes in a single region of the body and disseminated TB as existing when two or more organs were affected by the disease.

Bacteriology

Lymph nodes were thinly sliced, homogenized, crushed in a mortar, and then pretreated by the N-acetyl-L-cysteine–NaOH procedure, at an initial NaOH concentration of 3%. Tissues with negative results for bacterial growth after 48 h were not decontaminated. The sediment was resuspended in 2 mL of phosphate buffer solution (pH 6.8), and the suspension was used to prepare an acid-fast smear and culture. All specimens were screened with an auramine O fluorescent stain. Next, 0.5 mL of the solution was used to inoculate a mycobacterial growth indicator tube (MGIT) (Becton Dickinson), and 0.25 mL to inoculate Lowenstein–Jensen and Coletos (Biorad) culture media. Mycobacterial isolates were identified with specific DNA probes (Accuprobe bioMerieux).

Statistics

The groups were compared for quantitative variables with Fisher’s PLSD test or an unpaired t-test and for proportions with a chi² test or Fisher’s exact test (for 2×2 contingency tables). Differences were considered significant if the p-value was < 0.05.

Results

Patients (table I)

During the study period, the department saw 113 patients with LNTB. Complete data were available for 92, who were thus included in the study, while the 21 with incomplete data were not included. The most frequent reason for incomplete files was that patients were being followed in another hospital. Because Lariboisière Hospital hosts the emergency department for ear, nose, and throat diseases in Paris, patients with cervical lymph node disorders are frequently referred here for diagnostic procedures. These patients are subsequently sent back to their referring practitioner for follow-up at a later date.

Patients were natives of the following countries: Algeria 6, Brazil 1, France 12, Morocco 5, Poland 1, Portugal 1, Tunisia 3, all (n = 29) pooled in Group A (31.5%); China 1, India 6, Pakistan 8, Philippines 1, Sri Lanka 4, Turkey 1, Vietnam 1, all (n = 22) pooled in Group B (23.9%); and Angola 1, Cameroon 8, Congo 5, DR Congo 2, Ivory Coast 4, Ethiopia 1, Guinea Bissau 1, Guinea Conakry 1, Haiti 2, Lebanon 1, Madagascar 2, Mali 7, Mauritania 1, Rwanda 2, Senegal 2, and Zambie 1, all (n = 41) pooled in Group C (44.6%). There were 62 men and 30 women (mean age: 38.5 ± 15 years). Patients in groups B (35.5 years old) and C (35.7 years old) were significantly younger than those in group A (44.7 years old) (p = 0.02).

Tuberculosis disease and associated conditions (table II)

All patients were tested for HIV; 24 (26%) were HIV-infected, 20 of them (83%) from group C. The HIV diagnosis followed the TB diagnosis in 15 of these 24 patients overall (62.5%) and in
13 of the 20 (65%) from sub-Saharan Africa. Nine patients (47.5%) had been diagnosed with HIV infection 45 months (median) before presentation with LNTB. TB was the first AIDS-classifying event for these 9 patients. One had a history of adequately treated TB, and 8 reported close contact with someone known to have TB, from 8 months to 14 years ago. Localized LNTB was identified in 36 (39%) and disseminated TB in 56 (61%) patients (Table III). TB was defined as disseminated in 41% of group A, 68% of group B, and 71% of group C patients ($p = 0.034$). Among the 24 HIV-infected patients, TB was localized in 4/24 (17%), and among those HIV-negative, it was localized in 32/68 (47%) and disseminated in 36/68 (53%) ($p = 0.01$). In HIV-infected patients, the median CD4 count was 162 cells/µL [interquartile range (IQR) 134–210] in LNTB and 85 cells/µL [IQR 47–164] in disseminated TB. Men had disseminated disease significantly more often than women, regardless of HIV status ($p = 0.0002$): men accounted for 31/36 (86%) of disseminated TB cases among patients without HIV infection and 15/20 (75%) of those with HIV infection. On the other hand, among those with localized LNTB, women accounted for 18/32 (56%) of HIV-negative and 2/4 (50%) of HIV-negative patients.

### Table I
Demographic characteristics of patients according to geographic classification.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Total</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>29 (31.5)</td>
<td>22 (23.9)</td>
<td>41 (44.6)</td>
<td>92 (100)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (52.2%)</td>
<td>15 (68.2%)</td>
<td>31 (75.6%)</td>
<td>62 (67.4%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Female</td>
<td>13 (44.8%)</td>
<td>7 (31.8%)</td>
<td>10 (24.4%)</td>
<td>30 (32.6%)</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>44.7</td>
<td>35.5</td>
<td>35.7</td>
<td>38.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>HIV coinfection</td>
<td>3 (10.3%)</td>
<td>1 (4.5%)</td>
<td>20 (48.8%)</td>
<td>24 (26%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>12 (41%)</td>
<td>15 (68%)</td>
<td>29 (70.7%)</td>
<td>56 (61%)</td>
<td>0.034*</td>
</tr>
</tbody>
</table>

*In relation with the HIV status according to the region of origin, separate analysis for the subgroup of HIV negative patients. $p$ value > 0.05.

### Table II
Patients’ characteristics according to human immunodeficiency virus (HIV) infection status.

<table>
<thead>
<tr>
<th></th>
<th>HIV negative 68 patients</th>
<th>HIV coinfected 24 patients</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) patients in group C versus group (A + B)</td>
<td>21/41 (51%) versus 47/51 (92%)</td>
<td>20/41 (49%) versus 4/51 (8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex distribution male</td>
<td>45/68 (66%)</td>
<td>17/24 (71%)</td>
<td>ns</td>
</tr>
<tr>
<td>Number (%) of patients with disseminated disease</td>
<td>36/68 (53%)</td>
<td>20/24 (83%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number (%) of patients admitted</td>
<td>15/68 (22%)</td>
<td>23/24 (96%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean (range) duration of admission in days</td>
<td>20 (1–60) days</td>
<td>32 (4–150) days</td>
<td>0.039</td>
</tr>
</tbody>
</table>

### Table III
Comparison of disseminated tuberculosis (TB) disease versus lymph node TB disease.

<table>
<thead>
<tr>
<th></th>
<th>Disseminated 56 patients</th>
<th>Lymph node TB 36 patients</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution male versus female</td>
<td>46/62 (74%) men 10/30 (33%) women</td>
<td>16/62 (26%) men 20/30 (67%) women</td>
<td>0.0002</td>
</tr>
<tr>
<td>Admission</td>
<td>53/56 (95%)</td>
<td>23/36 (64%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Number (%) of patients with systemic symptoms</td>
<td>51/56 (91%)</td>
<td>21/36 (58%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Mean (range) C reactive protein in mg/dL</td>
<td>69 (6–288)</td>
<td>41 (4–219)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Of the 56 patients diagnosed with disseminated TB, 38 (68%) had MTB identified by either sputum smears or cultures, 5 (9%) had sputum specimens that were negative on smears and cultures, and 13 (23%) patients had no specific sputum examination. In addition, MTB was identified in the following samples:
- ascitic fluid: 3;
- urine specimen: 3;
- retropharyngeal abscess: 1;
- gastric aspirate: 2;
- cerebrospinal fluid: 2;
- liver biopsy: 1;
- and preternal abscess: 1.
Of the 36 patients diagnosed with localized TB, respiratory specimens of 12 were negative for MTB, sputum smears or cultures were positive for 2, and none were examined for 22. MTB was also identified in the urine of one LNTB patient.
Overall, 66 of 92 (71%) patients presented with superficial LNTB in the following locations:
- cervical: 48/66 (73%);
- suprACLavicular: 20/66 (30%);
- axillary: 16/66 (24%);
- inguinal: 11/66 (17%).
A single LN site was affected for 46 patients, 2 for 13, and 3 or more for 7. Visceral LNs were affected in 26 (28%) patients. Finally, 29/92 (31%) patients had pulmonary symptoms simultaneously with superficial or visceral lymphadenitis. Only 64% of patients with localized LNTB were admitted to the hospital, compared with 95% of those with disseminated TB ($p < 0.05$). HIV-infected patients had significantly longer hospitalizations than those without HIV infection. Disseminated TB was also associated with more severe inflammatory syndromes and more systemic disorders, compared with localized LNTB.

**Diagnostic procedures**
Diagnostic procedures included clinical examinations, chest radiographs and other imaging investigations as required by the clinical presentation, aspiration/biopsy of LN, pathology examinations and the culture of specimens for MTB.
Bacteriologic results for the 70/92 patients who underwent LN procedures, either fine needle aspiration (FNA), lymph node biopsy or some combination of both, were as follows: of 36 FNA samples, smears were positive in 58% and cultures in 92%; of 20 biopsy specimens, smears were positive in 30% and cultures in 85%; and of the 14 patients who underwent FNA and then had a biopsy, biopsy smears were positive in 29% and cultures (from either of the two procedures) in 93%. For the remaining 22 patients, the diagnosis was based on the identification of MTB in a site other than a LN. Of 57 pathology examinations, 34 (60%) showed macroscopically visible caseous necrosis (28 cases), acid-fast bacilli (AFB) (6 cases), or granulomatous adenitis (13 cases), and there were no significant differences between individuals with or without HIV infection, or between those with localized or disseminated TB.
MTB was sought in sites other than LN in 65 (71%) patients, based on clinical symptoms or signs; it was identified in 77% (50/65), including 39 sputum specimens. Fifteen of 24 (62%) HIV-infected patients and 27/68 (40%) HIV-negative had a smear positive for AFB, regardless of the sample site ($p = 0.06$). Among the HIV-infected patients, the median CD4 count was similar in patients with AFB-positive smears: 86 cells/µL [IQR 35–160] and those with AFB-negative smears: 87 cells/µL [IQR 68–173].

**Treatment and outcome**
Either 4-drug (in 78 patients) or 3-drug (in 14 patients) regimens were administered for a 2-month intensive phase, followed by a continuation phase of different durations. The median length of treatment was 7.5 months. Duration of therapy was significantly longer in patients with disseminated TB: 60%, compared with 32% of patients with localized LNTB, were treated for longer than 9 months ($p = 0.037$). Treatment also exceeded 9 months for 79% of the HIV-infected patients compared with 39% of those without HIV infection ($p = 0.014$).
No patients received directly observed therapy.
Clinical condition worsened due to paradoxical reactions in 22 patients (24%), including 6 who received steroids. Six of 24 (25%) TB/HIV coinfected patients had paradoxical reactions, including 2 who received steroids. All coinfected patients received antiretroviral therapy during TB treatment. The median CD4 count increased from 77 cells/µL [IQR 65–162] to 220 cells/µL [IQR 164–276] after 6 months of TB treatment. Their median viral load was 92,700 copies/mL [IQR 30600–123000] at TB diagnosis. Only 4 patients had viral load measured after 6 months of TB treatment, and it was undetectable in 3. Eleven additional TB/HIV coinfected patients received antiretroviral therapy during TB treatment without developing a paradoxical reaction.
According to WHO, the TB treatment outcomes are: cure, treatment completion, death, default, failure, or transfer out. A patient is considered to have interrupted treatment, that is, to have “defaulted” if he or she stopped treatment for 2 consecutive months or more. We defined as “defaulters” patients not seen at consultation for at least 2 months and for whom we had no information about transfer to another hospital. In all 67 (74%) patients were cured or completed treatment, 3 (3%), one with HIV infection, died of a TB-related cause, 3 (3%) relapsed, and 19 (20%) defaulted. Default was not associated with geographical group or HIV status.

**Discussion**
As in other western European series, most of the newly diagnosed TB and TB/HIV coinfected patients were natives
of countries with a high burden of one or both diseases [15]. Native French TB patients were older than foreign-born patients and usually had no underlying disease [16]. We found HIV coinfection in 4% of patients from India and Pakistan and in 49% of those from sub-Saharan Africa. Previous studies have reported TB/HIV coinfection rates of 8% in an Indian series of LNTB [17] and from 22% [18] to 84% [19] in series from sub-Saharan Africa. TB/HIV patients with disseminated TB also have a lower median CD4 count than those with localized LNTB. In an Indian series, only disseminated TB was predictive of low CD4 count [20]. According to WHO guidelines for HIV clinical staging, patients presenting with isolated LNTB should be categorized as clinical stage 3, while all other extrapulmonary TB patients are stage 4 [21].

Systemic symptoms, inflammatory syndrome, and rate and duration of hospitalization were more frequent in patients with disseminated TB and with HIV. Patients with localized LNTB usually had few constitutional symptoms [22]. As in our series, TB patients in the literature are more often men than women. A Mexican series observed a higher rate of transmitted and reactivated disease, more severe disease, and poorer treatment outcomes in men than women [23]. Multiple factors might be responsible for the sex imbalance in TB patients [24].

LNTB is a diagnostic challenge in resource-limited settings, where a high rate of HIV coinfection means that numerous other causes of LN enlargement are possible [25–27]. WHO guidelines for the diagnosis of LNTB recommend performing FNA and if necessary a biopsy [28]. The yield of diagnostic procedures has been shown to vary, according to the HIV status of the patients. HIV-infected patients frequently lack granulomas with caseous necrosis [17], but may have smears positive for AFB more often than HIV-negative patients [29]. In an Ethiopian series, most of the patients were diagnosed by FNA cytology and AFB smear examinations [18]. In our series, about 90% of cultures from FNA or biopsy samples were positive for MTB. In keeping with results from other studies, the yield from cultures was much higher than from direct smear examination from FNA or biopsies. This again demonstrates the need for routine cultures, which are also the only way to perform drug sensitivity testing [30] in this era of emerging multi-drug resistant MTB. Systematic cultures of sites other than lymph nodes, such as sputum, urine, or even stool [31], are an important adjunct to the diagnosis. We found a high proportion of disseminated TB even in HIV-negative patients. In another series, 20% of patients presenting with apparently localized head and neck tuberculosis had another active TB site [32]. An Asian series of LNTB found that about 60% of the patients had sputum specimen smears positive for AFB [33]. Although HIV-infected patients generally develop disseminated TB disease more frequently, in our series, more than 50% of HIV-negative patients also presented with disseminated TB. Consistent with published data on LNTB [14], 24% of our patients had a paradoxical reaction during TB treatment. The same regimens are recommended to treat pulmonary and extra-pulmonary TB, and treatment response is reported to be similar in patients with or without HIV infection [34]. Most patients in our series were not treated according to the guidelines in that the length of treatment exceeded guidelines. This finding is consistent with the previous report of a high rate of prolonged treatment, mostly for extrapulmonary TB, in France [35].

Our mortality rate (3%) is much lower than that reported in other series, especially for HIV-infected patients [36,37]. Our treatment success rate is in the same range, compared with the 72% success rate in another non-DOTS area in Europe [38]. In our series, the reported rate of patients lost to follow-up is consistent with the results of a large cohort of TB patients treated in French hospitals [39]. The DOTS strategy has been shown to improve treatment outcome substantially [40]. In France, the reporting of TB disease has been mandatory since 1964, but there is no national system to trace defaulting TB patients. Reporting treatment outcome to the French health authorities has been mandatory only since 2007 [41].

http://www.sante.gouv.fr/htm/dossiers/cshpf/a_mt_190506_tuberculose.pdfTB/HIV patients were diagnosed at a late stage of the disease, as shown by their low CD4 counts. TB and HIV screening should be offered to emigrants from high burden countries to provide them with timely diagnosis and adequate treatment or prophylaxis [15,42]. The retrospective nature of our study prevented us from comparing the diagnostic yield of LN aspiration and biopsy, as they were performed on different patients. The detailed analysis of treatment outcome was hampered by the high number of patients lost to follow-up.

**Conclusion**

Taking patients’ country of origin into account can help in the differential diagnosis of lymph node pathologies according to their respective frequencies among natives of specific countries. HIV coinfection rates reflect the HIV prevalence in the country of origin, and HIV testing should be conducted in all TB patients, according to an “opt-out approach”. Disseminated TB is frequent in all patients with LNTB, and even more so in HIV coinfected patients. Smear microscopy is insufficient for an accurate diagnosis. MTB cultures from FNA or biopsy or other specimens are important for diagnosis. TB control must be improved in France to reach the 85% cure rate targeted by the World Health Organization. Therapeutic guidelines, in particular length of treatment and bacteriologic follow-up, should be adequately implemented in French hospitals. DOTS or similar strategies should be evaluated to reduce the number of patients who interrupt therapy or become lost to follow-up.

Conflicts of interest: none.
References


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[41] Avis du conseil supérieur d’hygiène publique de France. Section Maladies transmissibles.

Relatif à la déclaration obligatoire des issues de traitement dans la tuberculose maladie.