Epidemiological, therapeutic and evolutionary profiles in patients with lymph node tuberculosis

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ÖZET

Lenf bezi tüberkülozu olan hastalarda epidemiyolojik, terapötik ve gelişimsel profiller

Tüberküloz özellikle üçüncü dünya ülkelerinde bir toplum sağlığı sorunu olmayı sürdürmektedir. Lenf bezi tüberküloz en sık görülen akciğer dışı yerleşim alanıdır. Gelişmekte olan ülkelerden gelişmiş olanlara modern taşıma ve göçlerden dolayı, tüm klinisyenler için bu tanı olasılığını akılda tutmak önemlidir. Lenf bezi tüberkülozu doğrulanmış hastalarda tedavinin yanı sıra demografik özellikler, tanısal yaklaşımlar, terapötik yaklaşımlar ve gelişimsel yönlerinin değerlendirilmesi amaçlanmıştır. Dört yıllık süre boyunca Rabat'ta 2 merkezden 69 hastanın verileri retrospektif olarak incelendi. Hastalarda kadın (%70) ve genç yaş hakimiyeti vardı. Medyan semptom başlangıç süresi ve tanı süresi uzundu: 115 gün (interquartile range 34-150 gün), bu durum düşük sosyoekonomik şartlarla açıklandı (p< 0.05). En sık tutulan servikal lenf bezleriydi (%85.5). Tanı %98.5 histolojik, %1.5 lenf bezi aspirasyonundan bakteriyel olarak konuldu. Hastaların %48'i ulusal tüberküloz rehberine göre tedavi edilmişti. Hastaların yarısı paradoksik yanıt nedeniyle yedi buçuk aylık (7.3 month +/-1.3) uzamış tedavi almışlardı (p< 0.05). Tedavi bitiminde lenf nodları hastaların %80'inde normal boyutlarına dönmüştü, %11.6'sında rezidüel lenf bezi ve %8.6'sında scrofula saptadık. Lenf bezi tüberkülozunun tanısında gecikme halen önemlidir ve tedavi paradoksik yanıt nedeniyle uzamaktadır.

Anahtar Kelimeler: *Lenf bezi tüberkülozu, epidemiyoloji, tedavi, gelişim.*

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Tuberculosis remains a public health concern worldwide particularly in Third World countries. Lymph node (LN) tuberculosis is the most frequent extra lung localization. Because of modern transport and mass migration from the developing to the developed world, it is important for all clinicians to keep this diagnostic possibility in mind. Evaluate demographic characteristics, diagnosis approaches, therapeutic strategies and evolutionary aspects while treatment in patients with confirmed LN tuberculosis. Data were retrospectively analyzed in 69 patients collected in 2 health centers in Rabat over a period of 4 years. There was a female (70%) and a young age predominance of patients (31.4 year +/-13.1). The median duration between the onset of symptoms and diagnosis was long: 115 days (interquartile range 34-150 days) explicated by low Socioeconomic conditions (p< 0.05). The cervical LN were most frequently involved (85.5%). The confirmation was histological in 98.5%, bacterial in the liquid from puncture LN in 1.5% of cases. 48% of patients had received treatment according to the national guide of tuberculosis. Half of the patients had received prolonged treatment on average of 7 months and a half (7.3 month +/-1.3) because of the paradoxical response (PR) (p< 0.05). At the end of treatment, LN had returned to their normal size in 80% of patients, we noted residual nodes in 11.6%, and a scrofula in 8.6%. The delay of diagnosis of LN tuberculosis is still important, and the treatment is prolonged because of PR.

Key Words: *Lymph node tuberculosis, epidemiology, treatment, evolution.*

Tuberculosis remains a public health concern worldwide particularly in Third World countries. In 2008, 25.325 new cases were reported in Morocco which corresponds to 81 new case per 100.000 residents (1).

In Morocco, the Struggle against tuberculosis is one of the priorities of Ministry of Health, that's why a national tuberculosis control programme fully funded by the Moroccan government has been instituted for more than 40 years. Morocco was also one of the first countries to adopt the DOTS (directly observed treatment, short-course) strategy in the early 1990s and the results were very satisfactory (2).

Dispensaries and health centers represents the leading of this strategy providing consultation and treatment at no cost to patients.

Among extra pulmonary tuberculosis, lymph nodal localization is the most frequent (about 50%). Until now very little clinical information has been available on lymph node (LN) tuberculosis from Morocco.

Because of modern transport and mass migration from the developing to the developed world, it is important for all clinicians to keep this diagnostic possibility in mind.

The aim of the study is to evaluate demographic characteristics, diagnosis approaches, therapeutic strategies and evolutionary aspects while treatment in patients with confirmed LN tuberculosis.

MATERIALS and METHODS

Study Population

This study involved a retrospective analysis of records of 69 patients collected in 2 centers of health in Rabat over a period of 4 years (January 2004 to December 2007) with LN tuberculosis.

Inclusion criteria: Patients with confirmed tuberculosis: The diagnosis was retained when:

The evidence was supported by histology (biopsy of a LN) which shows a caseating granulomas with necrosis.

The evidence was supported by bacteriology [fine needle aspiration (FNA)] which shows acid-fast bacilli on Ziehl-Neelsen.

Exclusion criteria: Patients with no confirmed LN tuberculosis:

Non-caseating granulomatous disease.

Age less than 14 years.

Patients on treatment for tuberculosis or receiving corticosteroids, immunosuppressive, or anti-retroviral therapy.

Detailed information was recorded: epidemiological characteristics (age, sex, socio-economic conditions whose criteria to discriminate between low and medium was a salary lower than $200 per month and or illiteracy, antecedents, status of contact with active tuberculosis cases), clinical history and presentation while diagnostic (constitutional symptoms including fever, sweating, weight loss, weakness, respiratory symptoms and characteristics of LN), the median duration between the onset of symptoms and diagnosis, results of tuberculin test, microbiologic, radiologic, and histopathologic findings, treatment regimen, treatment duration, drug side effects, and evolution while treatment in particular paradoxical response (PR).

PR was defined as a worsening of pre-existing tuberculosis lesions, based on clinical or radiological findings, or the development of new lesions, in patients who had received anti-tuberculosis treatment for at least 2 weeks and who seemed to be improving initially. The time to onset of PR was defined as the number of days from the start of treatment to the commencement of lymphadenopathic deterioration (3).

Statistical Analysis

Data entry and analysis was done using SPSS 13.0 for Windows® (SPSS Inc, Chicago, IL, USA). Data were expressed as mean ± standard deviation and range, and for data with skewed distribution as median and range. The Chi2 test was used to evaluate correlations between categorical variables. Relationships among continuous variables were evaluated using Student's t test. Differences were considered statistically significant if p was less than 0.05.

RESULTS

Epidemiology

During the 4 year study period, a total of 69 patients with confirmed LN tuberculosis were enrolled in the study.

The mean age of patients was 31.4 year +/-13.1, and 48 (70%) patients were female. 47 (68%)patients had a low Socioeconomic conditions.

Predisposing factors were found: 2 (3%) patients were HIV positive, one (1.5%) was infected by virus of hepatitis C, one (1.5%) was diabetic, and 2 (3%) were alcoholic.

2 (3%)patients were already treated for tuberculosis (both pulmonary localization). Contact history with tuberculosis cases was elicited in 10 patients (14.5%).

The patients' characteristics are represented by the Table 1.

Table 1. Patients' characteristics*

Characteristics (n= 69)	Patients, no (values)
Epidemiology:	
Age	31.4 [+/-13.1 (14-60)]
Sex	
Male	21 (30)
Female	48 (70)
Socioeconomic conditions	
Low	47 (68)
Medium	22 (32)
Contact history with tuberculosis cases	10 (14.5)
Already treated for tuberculosis	2 (3)
Risk factors	
HIV	2 (3)
HVC	1 (1.5)
Diabetes	1 (1.5)
Alcohol	2 (3)

* Values given as % or mean +/- Standart deviation (range).
HIV: Human immunodeficiency virus, HVC: Hepatitis viral C.

The median time that had elapsed between the onset of symptoms and presentation was 115 days (min-max range 4-540 days). The median delayed time was 119 days (min-max range 15-540) in low socioeconomic conditions versus 71 days (min-max range 4-150) in median socioeconomic conditions with statistically significant difference (p< 0.05).

Clinical and Laboratory Findings (Table 2)

Constitutional symptoms including fever, sweating, weight loss, weakness were found in 7 patients (10%).

Respiratory signs were found in 2 (3%) patients represented by cough with expectoration.

Tuberculosis most frequently affected the cervical LN (85.5%), followed by the subclavicular LN (11.5%), the axillary associated to mediastinal LN (1.5%) and the inguinal LN (1.5%).

The LN were unilateral in 59 (85.5%) patients.

11 (16%) patients had painful LN, 10 (14.5%) patients had inflammatory signs without fistulization and 6 (8.5%) patients had inflammatory signs with fistulization.

Table 2. Clinical and laboratory findings.

Clinical and laboratory findings (n= 69)	Patients, no (%)
Clinical findings:	
Night sweats, weight loss, and weakness	7 (10)
Respiratory signs	2 (3)
Lymph node:	
Unilateral	59 (85.5)
Localization:	
Cervical	59 (85.5)
Subclavicular	8 (11.5)
Axillary associated to mediastinal	1 (1.5)
Inguinal	1 (1.5)
Painful	11 (16)
Inflammatory signs without fistulization	10 (14.5)
Inflammatory signs with fistulization	6 (8.5)
Laboratory findings:	
Sputum sample tests	2 (3)
Tuberculin test:	
Done	40 (58)
> 14 mm	32 (80)
6-14	2 (5)
< 6 mm	6 (15)
X chest radio:	
Done	47 (68)
Normal	44 (94)
Radiographic abnormalities	3 (6)
Confirmation of lymph node tuberculosis:	
Histological	68 (98.5)
Bacterial	1 (1.5)

Sputum sample tests were performed only on the two patients who had respiratory signs and cavitation on the X chest radio. It showed a microbiological evidence of active pulmonary tuberculosis.

Of the 69 patients, the tuberculin test was made in 40 (58%) patients. It was higher than 14 mm in 32 (80%) patients, less than 6 mm in 6 (15%) patients and between the 2 values in 2 (5%) patients.

The X chest radio was made in 47 (68%) patients, it was normal in 44 (93.6%) patients and 3 patients had radiographic abnormalities (2 cavitation and one mediastinal LN confirmed by a chest scan).

The confirmation was histological in 98.5% of cases (excision of the LN) which revealed a granuloma with multinucleated giant and epithelioid cells associated to caseous necrosis. The confirmation was also bacterial in the liquid from puncture LN (by FNA) in 1.5% of cases which isolated acid-fast bacilli on Ziehl-Neelsen completed by culture which identified the mycobacterium tuberculosis.

Therapy and Evolution

According to the national guide of struggle against tuberculosis which is inspired on the WHO recommendations, initial therapy was a combination of isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), and pyrazinamide (25 mg/kg/day) 6 days per week in 65 patients (94%) who were treated for the first time and for an extra lung localization (considered as category 3). The treatment was a combination of isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), pyrazinamide (25 mg/kg/day) and ethambutol (20 mg/kg/day) 6 days per week in 2 (3%) patients who were already treated for pulmonary tuberculosis (considered as category 2). Initial therapy was also a combination of isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), pyrazinamide (25 mg/kg/day) and streptomycin (15 mg/kg/day) 6 days per week in 2 (3%) patients who had a microbiological evidence of active pulmonary tuberculosis in sputum (considered as category 1). None of the patients required surgical treatment.

Minor drug-dependent side effects occurred in 10 (14.5%) patients as allergic reactions and gastrointestinal intolerance and received symptomatic treatment with a favorable evolution.

PR while treatment occurred in about half of patients (48%) at a median onset time of 9 weeks after starting the treatment (min-max range 5-14.5). Of these patients, 22 (32%) presented with enlarged LN without local inflammatory signs, 3 (4%) patients presented with enlarged LN with local inflammatory signs, 5 (7%) patients presented with development of new LN, and 3 (4%) patients with fistulization.

No statistically significant differences were found between comparing patients with and without PR (comparison was made on age, sex, socioeconomic conditions and the presence of local tenderness at the time of diagnosis: pain, inflammatory signs with or without fistulization) The mean duration of the treatment was 7.3 month +/-1.3. The prolongation of the treatment was beyond 6 months related to the paradoxical response: enlargement of LN with or without inflammatory signs in 7% ($p < 0.05$), development of new LN with or without inflammatory signs in 4.5% ($p < 0.05$), and fistulization in 4.5% ($p < 0.05$).

We noted residual nodes in 11.5%, and a scrofula in 8.5% of patients after completion of therapy.

DISCUSSION

Tuberculosis remains one of the most fatal diseases in the world. Both women and men are affected by this disease and all age groups are concerned, especially young adults. Indeed, 70% of the patients are aged between 15 and 45 years, hence the risk of economic and Social potential loss because it affects the most productive age group population (4).

The incidence of extrapulmonary tuberculosis has been increasing worldwide over the last few years (5,6). Peripheral LN tuberculosis is observed in about 5% of all tuberculosis patients and 25 to 60% of extrapulmonary tuberculosis cases, making it one of the most common forms of extrapulmonary tuberculosis (7-11).

We noted a female predominance in 70%, this result concords with those found in some other studies with a sex ratio varying between 0,28 and 0.73 (12-16). We found also a young age of patients (31.4 year +/-13.1) (17,18).

Incidence of tuberculosis rises under individual conditions such as leukemia, HIV, or diabetes which depress the immune system, and under socioeconomic conditions such as war, poverty, overcrowding, and migration (19,20). The risk factors found in our study were the low socioeconomic conditions (poverty and overcrowding) in 68%, HIV and hepatitis viral C infections, diabetes and alcoholism.

Involvement of cervical LN in patients VIH negative are the most commonly affected group in about 70 to 87% of cases (21-25). In our study the tuberculous infection most frequently affected the cervical LN (85.5%).

6 (9%) patients had inflammatory signs with fistulization. Lacut and al found nearly the same results (10%) (26).

At the time of diagnostic, night sweats, weight loss, and weakness were found in (10%) which is less than the results found in literature: night sweats found in 40 to 78%, weight loss in 33 to 85% (19).

Respiratory signs where found in 2 (3%) patients represented by cough with expectoration, explicated by the association with active pulmonary tuberculosis.

The long mean time (nearly 4 months) that had elapsed between the onset of symptoms and presentation is explicated by low Socioeconomic conditions which lead the patients to not to consult (p< 0.05).

In Morocco, testing for HIV is not routinely done in the centers of health; therefore, no information on HIV status was present in the records.

The tuberculin skin test is habitually positive in case of LN tuberculosis: 63 to 90% in the literature (23). In our study, it was positive in 80% of the patients who did it. However, the negativity of this exam does not eliminate the diagnosis of evolutive LN tuberculosis, particularly in patients infected with HIV (IDR positive in only 15% to 33%) (19-24). In our study patients who were infected by HIV and HVC had the tuberculin skin test negative.

Whereas it is a common practice to obtain a chest radiograph for all patients with extra pulmonary tuberculosis (in our study it was made in 68% of the patients), sputum examinations are typically limited to those with abnormal radiographic findings that are suggestive of pulmonary tuberculosis (in our study it was limited for the 2 person who had cavitation on the chest radiograph). Parimon and Al found that sputum examination may nonetheless identify subclinical involvement of the respiratory system with tuberculosis (27).

Excisionnal biopsy still has an important place in the diagnosis of cervical LN tuberculosis (24,28). First because in the (FNA), the highlight of fast acid bacilli on zeel Nielson is less than 30% and the culture is more positive after biopsy compared to it (77% versus 40%) (19). The (FNA) is then considered less effective than excisionnal biopsy (29). Second the duration of diagnostic and treatment is prolonged with FNA (culture is more effective) (24). Third excision shows a specific histology: multinucleated giant and epithelioid cells associated to caseous necrosis in 90 to 100% of LN tuberculosis (26,14). However, FNA cytology has an important role in the evaluation of tuberculosis adenitis, as a non-invasive alternative to excisional biopsy and most patients including those with abscesses will respond to appropriate chemotherapy without excision biopsy (5,30). In our study 98,5% of patients have beneficed of the biopsy, versus 1.5% of FNA.

Whatever the method used, culture, identification and microbiologic sensitivity tests should be realized. Unfortunately it was not done at all in our study.

As concern the treatment, before the era of chemotherapy, surgical excision of all the LN was the main form of treatment. With the introduction of antituberculous chemotherapy in the 1950s, excision of all grossly involved LN followed by antituberculous chemotherapy from 12 to 24 months was found to be more

effective treatment. It was later found that LN excision was not necessary, and chemotherapy alone gradually became the standard treatment (31). The duration of chemotherapy has decreased during the years with the use of more effective bactericidal drugs (32-35). While some organizations, for example the WHO and the IUATLD recommend a 6-month regimen (a duration also endorsed by certain important journals, other guidelines propose a regimen of 9 to 12 months, although they do recognize that this recommendation is not supported by any evidence from randomized clinical trials (36-39).

According to the national guide of Struggle against tuberculosis, the total duration of treatment of LN tuberculosis is 6 months by chemotherapy.

In this study the mean duration of the treatment was 7.3 month +/-1.3. The prolongation of the treatment was beyond 6 months related to the PR.

In this study, as for Braune et al., it's essentially the clinical impression and evolution while treatment that determinate the treatment duration (40).

The indication of the surgery as therapeutic operation, in first-line treatment in the presence of a cold abscess, an inexhaustible fistula, lymphadenitis with atypical mycobacteria, and a large and calcified lymph-node mass for which medical treatment will not be sufficient, or in secondary surgery in the event of failure or progress under medical treatment or in case of residual adenopathy at the end of an appropriate medical treatment (28).

PR occurred in 33 (48%) patients at a median onset time of 9 weeks after starting the treatment. Cho and al have found a similar result than our study: 23% at a median onset time of 8 weeks (3).

Recent studies suggest that immunotherapy with steroids or an anti-TNF-α inhibitor may help to resolve paradoxal response by inhibiting granuloma formation interfering with penetration of anti-tuberculosis drugs (41,42). Further studies are needed to evaluate the adjunctive role of immunotherapy in patients at high risk for paradoxical response.

Residual nodes were noted in 4-10% of cases after completion of therapy (11.6% in our study) (5,43). Although most of them were free from microbiological relapse the treatment duration must then not exceed 6 months (35,44-46). It is crucial that clinicians carefully differentiate between post-therapy paradoxical expansion and treatment failure. Otherwise, patients may be subject to a higher risk of anti-tuberculosis drug-related side effects.

The main limitation of this study was that no case for whom a culture result was available. As a result, we used other diagnostic criteria: granulomatous inflammation with caseification necrosis by node excision or highlight fast acid bacilli in Zeel-Nielson, clinical and radiologic data, history of close contact with tuberculosis cases, and favorable response to treatment to establish diagnosis of LN tuberculosis in all the cases. However, lymphadenitis caused by non tuberculosis mycobacterium such as the Mycobacterium avium complex is rare in non-HIV adult patients (47).

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