LYMPH NODE TUBERCULOSIS: CLINICAL AND THERAPEUTIC APPROACH

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ABSTRACT

Background: Lymph node tuberculosis is currently a common pathology in Tunisia which generates significant morbidity and socio-economic cost.
Aim: to describe epidemiological, clinical and therapeutic features of lymph node tuberculosis.
Methods: Retrospective study over a period of 12 years carried out from January 2008 to December 2019 at the ENT department of Habib Thameur hospital in Tunis, including 276 patients who were admitted for lymph node tuberculosis.
Results: The mean age of patients was 35±18.3 years, with 36.9% reporting consumption of raw milk. Chronic adenopathy was the main reason for consultation, observed in 11.4% of patients. The most affected lymph node site was the level IIa (65.9%). Tuberculin intradermal reaction (IDR) was >10 mm in 68% of cases. Hypoechoic lymphadenopathy was found in 79.9% cases, while 72.4% cases showed necrotic lymph nodes on ultrasound. Fine needle aspiration (FNA) was performed for cytological and bacteriological purposes. It had a specificity of 100% and a sensitivity of 72.7%. Surgery was indicated for inconclusive cytology or pre-fistulized lymphadenopathy (12 cases). Diagnosis was cytological for 12 patients and histological for others. The search for other sites of infection was systematic. The sites found were: pulmonary in 1 case, tonsillar in 2 cases and nasopharyngeal in one case. Pre-therapeutic evaluation was conducted in all cases. Initial empiric treatment comprised a 4-drug regimen for a median duration of 8.8 months, with an intensive phase of 2 months, followed by a continuation phase of 7 months (isoniazid and rifampicin). Medical treatment was prolonged for patients with drug resistance or poor clinical responses. During treatment, 11.2% of patients had presented side effects related to antitubercular medication. A paradoxical reaction was observed in 8.3% of cases. Drug resistance was observed in 14.8% cases. Univariate analysis identified predictive factors for prolonged treatment (>9 months): history of treated lymph node tuberculosis and bilateral lymphadenopathy. Recurrence rate was 2.5%, with clinical cure achieved in all cases after a mean time of 8.8 months.
Conclusion: Due to the low contribution of bacteriology and the high rate of inconclusive cytology, surgery remains important in the management of lymph node tuberculosis in association with medical treatment.
Keywords: Tuberculosis - Cervical lymphadenopathy - Adenectomy - Lymph node dissection - Antitubercular medications - Paradoxical reaction

RÉSUMÉ

Introduction: La tuberculose ganglionnaire est actuellement une pathologie courante en Tunisie, générant une morbidité significative et un coût socio-économique élevé.
Objectif: Décrire les caractéristiques épidémiologiques, cliniques et thérapeutiques de la tuberculose ganglionnaire.
Méthodes: Étude rétrospective sur une période de 12 ans, menée de janvier 2008 à décembre 2019 au service ORL de l'hôpital Habib Thameur à Tunis, incluant 276 patients admis pour une tuberculose ganglionnaire.
Résultats: L'âge moyen des patients était de 35±18.3 ans, avec 36.9% signalant une consommation de lait cru. L'adénopathie chronique était le principal motif de consultation, observée chez 11.4% des patients. Le site ganglionnaire le plus affecté était le secteur IIa (65.9%). L'intradermoréaction à la tuberculine (IDR) était >10 mm dans 68% des cas. A l'échographie, une adénopathie hypoéchogène a été retrouvée dans 79.9% des cas, tandis que 72.4% des cas présentaient des ganglions nécrotiques à l'échographie. Une cytoponction a été réalisée à des fins cytologiques et bactériologiques. Elle présentait une spécificité de 100% et une sensibilité de 72.7%. La chirurgie était indiquée en cas de cytologie non concluante ou d'adénopathie pré-fistulisée (12 cas). Le diagnostic était cytologique pour 12 patients et histologique pour les autres. La recherche d'autres sites d'infection était systématique. Les sites trouvés étaient: pulmonaire (1 cas), amygdalien (2 cas) et nasopharyngé (1 cas). Une évaluation pré-thérapeutique a été réalisée dans tous les cas. Le traitement empirique initial comprenait une quadrithérapie pendant une durée moyenne de 8.8 mois, avec une phase d'attaque de 2 mois, suivie d'une phase de consolidation de 7 mois (isoniazide et rifampicine). Le traitement médical était prolongé chez les patients présentant une résistance médicamenteuse ou des réponses cliniques insuffisantes. Pendant le traitement, 11.2% des patients ont présenté des effets secondaires liés aux médicaments antituberculeux. Une réaction paradoxale a été observée chez 8.3% des cas. Une résistance

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médicamenteuse a été observée dans 14.8% des cas. L'analyse univariée a identifié des facteurs prédictifs de traitement prolongé (>9 mois): les antécédents de tuberculose ganglionnaire traitée et les adénopathies bilatérales. Le taux de récidive était de 2.5%, avec une guérison clinique obtenue dans tous les cas après un recul moyen de 8.8 mois.

Conclusion: En raison de la faible contribution de la bactériologie et du taux élevé de cytologie non concluante, la chirurgie demeure importante dans la prise en charge de la tuberculose ganglionnaire en association avec le traitement médical.

Mots-clés: Tuberculose - adénopathie cervicale - Adénectomie - Dissection ganglionnaire - Médicaments antituberculeux - Réaction paradoxale

INTRODUCTION:

Lymph node tuberculosis (LNT) is currently a common pathology in Tunisia with an incidence rate of 18/100,000 in 2017 [1]. It generates significant morbidity and socio-economic cost. It's therefore a diagnostic and therapeutic challenge.

The aim of this study was to describe the epidemiological, clinical and therapeutic features of lymph node tuberculosis.

Methodology:

We report a retrospective descriptive study on 276 patients followed and operated on for LNT in the Otorhinolaryngology (ENT) and Cervicofacial Surgery (CFS) department of the Habib Thameur hospital in Tunis over a period of 10 years [January 2008 - December 2017].

We included all hospitalized and operated patients whose diagnosis of lymph node tuberculosis was retained by cytological and/or bacteriological examination on lymph node puncture fluid or by histological examination on surgical specimen.

We excluded patients with incomplete medical records and those lost to follow-up during treatment. Additionally, we did not include patients treated solely as outpatients for lymph node tuberculosis during the same period.

Data was collected from medical records. These data were entered and processed using SPSS version 20.0 software. The statistical processing of the data consisted of two parts; the first was purely descriptive, the second analytical:

Descriptive study: We calculated simple frequencies and relative frequencies (percentages) for the qualitative variables. We calculated means and standard deviations and determined the range (extreme values = minimum and maximum) for the quantitative variables.

Analytical study: The Chi2 test and the Student test were used respectively for the comparison of percentages and means. In all statistical tests, the significance level was set at 0.05.

In addition, we have defined certain clinical terms such as:

Resistance: is defined by the evolution of pre-existing adenopathies or the appearance of new adenopathies despite a well-conducted 9-month anti-tuberculosis treatment.

Recurrence: is defined by an increase in the size of a residual node or the appearance of one or more adenopathies after a complete course of anti-tuberculosis chemotherapy and a phase of clinical remission.

Healing: is defined by the absence of any sign of clinical and/or ultrasound progression at the end of the treatment.

Results:

The average age was 35 years +/- 18.3 with a sex ratio of 0.43. A family history of lymph node tuberculosis was found in 12 cases (4.34%). We found a history of treated tuberculosis in 6 patients (2.1%). It was pulmonary tuberculosis in 5 cases (1.8%) and digestive tuberculosis in one case. None of the patients was infected with HIV. Consumption of raw milk was found in 36.9% of cases. The reason for consultation was chronic swelling of one or more lymph nodes in all cases, it was fistulized in 11.4% of cases. Some patients presented ystematic symptoms like fever in 45 cases (16.3%), night sweats in 50 cases (18.1%), weight loss in 43 cases (15.6%) and asthenia in 23 cases. (8.3%). The adenopathies were unique in 173 cases (62.6%) and located at the level of the jugulo-carotid chain, in particular at the level of sector IIa (65.9%). (Table I)

Table I: Distribution of cervical adenopathies according to their location.

Seat	Number	Percentage (%)
Sector IIa (jugulo-carotid high prior)	182	65.9
Sector IIb (jugulo-carotid high posterior)	28	10.1
Sector III (middle jugulo-carotid)	53	19.2
Sector IV (lower jugulo-carotid)	29	10.5
Sector Ib (Submandibular)	36	13
Sector Ia (Submental)	6	2.2
Sector V (Spinal)	56	20.2

A second tuberculous localization was found in 4 cases (1.44%): it was pulmonary tuberculosis in one case, tonsillar tuberculosis in two cases and rhinopharengeal tuberculosis in one case. The tuberculin skin test was performed in 234 patients (84.78%), it was positive in 68% of cases. Systematic chest X-ray revealed sequelae lesions in 3 cases (1.08%) and active lesions of pulmonary tuberculosis in one case. Ultrasound examination was the first line test in all cases. The sonographic features where Hypoechoic 79.7%,

heterogeneous 17.3%, calcifications 6.8%, necrosis 72.4%. Single lymphadenopathy was found in 38.5% of cases and multiple in 61.5% of cases. Cervical CT was performed in 11.6% of cases. It was requested for the exploration of deep lymph node groups and in the event of voluminous lymphadenopathy to determine the relationship with the vascular axes.

The bacteriological study, which included a direct examination to detect Acid-Fast Bacilli (AFB), culture on Lowenstein medium, and germ identification by PCR, was conducted on two types of samples: cytological puncture fluid (in 46% of FNA cases) and ground lymph nodes (in 34.7% of surgical samples). However, this bacteriological study yielded negative results in all cases. The cytological examination of lymph node puncture fluid was performed systematically. The diagnosis was confirmed in 12 cases (4.34%) by demonstrating an epithelioid and giant cell granuloma with caseation (Table II). The specificity and sensitivity of FNA were 100% and 72.7%, respectively.

All patients underwent cervicotomy. Therapeutic cervicotomy was performed in the 12 cases diagnosed by FNA, which presented with fistulized adenopathy requiring surgical excision. In other cases, cervicotomy was performed for diagnostic purposes. Postoperative follow-up revealed lymphorrhea in 2 cases and transient paresis of the mental branch in 2 cases.

Table II: Results of the cytological examination after lymph node aspiration cytology

Cytology results	Number of cases	Percentage
Epithelioid granuloma with necrosis	12	4.3%
Epithelioid granuloma without necrosis or necrosis without granuloma	124	45%
Reactional	13	4.7%
suspected of malignancy	5	1.8%
Inconclusive	106	38.4%
Suppurative adenitis	16	5.8%

A pre-therapeutic assessment was made before the initiation of anti-tuberculosis treatment including a blood count (NFS), a liver test (ASAT, ALAT, bilirubinemia, TP), a cholestasis test (Gamma GT and alkaline phosphatases), a kidney test (creatinine), uricemia, liminal tonal audiometry with tympanometry if streptomycin is prescribed, an ophthalmological examination including a visual field as well as an evaluation of color vision (prior to prescription of ethambutol). The treatment was based on a quadruple therapy combining isoniazid, rifampicin, pyrazinamide and ethambutol for an average duration of 8.8 months, including an average of 2 months of quadruple therapy and 7 months of dual therapy (isoniazid and rifampicin). After treatment initiation, 199 patients (72, 1%) had an acetylation test to adjust the isoniazid dosage; We found 22% slow acetylators and 18% fast acetylators. The combined form was prescribed in 43.8% of cases. In the other cases, dissociated forms had been used in the presence of contraindications to one of the products, adverse effects or slow or fast acetylators.

During the medical treatment, the patients were followed monthly at our consultation and this through a meticulous interrogation, a clinical examination and a blood test including a dosage of transaminases, creatinine, uric acid and an NFS. We noted the occurrence of complications during treatment in 31 cases (11.2%) such as skin rash, hyperuricemia, hepatotoxicity, etc. (Table III)

Table III: Complications of anti-tuberculosis treatment

Complication	Number of cases	To behave
Skin rash	6	Combination of a treatment Antihistamine
Digestive disorders	1	Continuation of treatment
Hepatotoxicity	6	-Adaptation of isoniazid doses (1 case) -Stop treatment for 15 days (1 case) -Monitoring (4 cases)
Hyperuricaemia	12	-Stop pyrazinamide (2 cases) -Hyperhydration (1 case) -Monitoring (9 cases)
Neutropenia	1	Continuation of treatment + Monitoring
Thrombocytopenia	2	-Stop treatment (1 case) -Monitoring (1 case)
Anemia	1	Adjuvant martial therapy

The paradoxical upgrading reaction to antibacillary drugs was found in 23 cases (8.3%). Fourteen patients were treated with surgery. 11 had undergone a simple adenectomy and 3 had a selective lymph node dissection. Tuberculosis treatment was continued in all cases. We did not use corticosteroid therapy. Resistance to anti-tuberculosis treatment was observed in 41 cases (14.8%). Our attitude was to prolong the treatment for an average duration of 4.2 months. The dual therapy had been extended beyond 9 months and we prescribed streptomycin in combination for a period of 2 months in one patient. Medical treatment was associated with lymph node dissection in 19 cases. The surgical specimen was sent for bacteriological examination with culture and antibiogram. Direct examination was positive in 4 cases and positive culture in one patient.

LNT recurrence happend in 7 cases (2,5%) after an average delay of 8.8 months + 6.1 [2 - 18 months]. Selective lymph node dissection was performed in all cases in association with anti-tuberculous antibiotherapy.

Healing was achieved in all cases after an average delay of 8.8 months [6-51 months].

The univariate study of the predictive factors of an extension of treatment (>9 months) retained 2 factors, which are: the history of treated lymph node tuberculosis and the presence of multiple and bilateral adenopathies. (Table IV)

Table IV: Univariate study of predictive factors for an extension of treatment (>9 months)

Variables	NOT (%)	P-value
Age	-<15 years: 43 (15%) -15-65 years: 194 (71.1%) ->65 years: 7 (3.9%)	0.5035
Personal history of lymph node tuberculosis treated	-Yes: 9 (3.3%) -No: 267 (96.7%)	0.0004
ATCD TB staff treated	-Yes: 14 (5.1%) -No: 262 (94.9%)	3.0203
Diabetes	Yes: 11 (4%) -No: 265 (96%)	0.9545
Consultation period	-<3 months: 110 (44.1%) ->3 months: 162 (65.9%)	0.6940
Bilateral lymphadenopathy	-Unilateral: 245 (89.4%) -Bilateral: 29 (10.6%)	0.0098
Fistulized facing skin	-Yes: 31 (11.4%) -No: 241 (88.6%)	0.9470
Associated pulmonary tuberculosis	-Yes: 2 (0.8%) -No: 276 (99.2%)	0.3522
Size of largest adenopathy	-<30mm: 182 (65.9%) ->30mm: 85 (30.7%)	0.4926
Number of lymphadenopathy on ultrasound	-Single: 173 (63.6% -Multiples: 99 (36.4%)	0.1962
type of treatment	- Combined: 114 (43.8%) -Classic: 146 (56.2%)	0.329
Compliance to treatment	-Good: 252 (95%) -Bad: 14 (5%)	0.076

DISCUSSION :

Despite the program established by the UN to eradicate tuberculosis, this pathology is still relevant. Extra-pulmonary tuberculosis represents 62% of cases. The incidence has increased following the increase in the number of AIDS patients [1] and the consumption of raw milk, especially in developing countries. Nodal localization is the most frequent localization with predominance of cervical forms (47 to 98% of cases) [2]. Cervical swelling represents the first circumstance of discovery of LNT, followed by the appearance of a cutaneous fistula. Signs of tuberculous impregnation can occur sometimes, which seem to be predominant in the case of HIV seropositivity [3]. The typical adenopathy is most often located in the jugulo-carotid chain, and is firm, mobile, painless, unilateral and less than 30 mm in size [4,5]. In our study, we had a clear predominance of group IIa (76%). The predominance of the jugulo-carotid chain could be explained by the fact that the portal of entry for the Bacillus of Koch (BK) is typically buccopharyngeal.The adenopathy would represent a satellite node of the inoculation chancre [6]. The tuberculin IDR is an excellent test in developing countries because of its low cost and availability, but the results of this test must be interpreted according to the epidemiological context and the vaccination program of each country. The sensitivity of this test varies in the literature between 78% and 95%. However, a decrease in sensitivity is observed in immunocompromised subjects who present more false negatives [7]. Specificity varies from 73 to 87%. There are also many false positives in countries where the BCG vaccine is mandatory because the test does not distinguish between previous contact with a Mycobacterium or with the BCG strain [8-10]. In our series, 68% of tuberculin IDRs were positive. Thus, faced with cervical lymphadenopathy, a positive tuberculin IDR does not confirm the diagnosis of lymph node tuberculosis. The cervical ultrasound represents the examination of 1st intention allowing both to confirm the lymph node nature, to specify the characteristics and the reports of the adenopathy. The most evocative aspect is that of a hypoechoic lymphadenopathy, of heterogeneous structure with a necrotic center [11]. At a late stage, one can find intracortical calcifications characteristic of granulomatous lymphadenopathy. An ultrasound check-up at the end of treatment is also useful to support the morphological evolution of tuberculous lymphadenopathy. Up to 11% residual lymphadenopathy has been reported at the end of treatment [12]. End of treatment ultrasound was performed in 73 cases (26.44%) in our study. Computed tomography (CT) is a second-line examination indicated in cases of diagnostic uncertainty or to specify the number, location, and size of the lymphadenopathies, as well as their relationship with vascular structures.

The formal explorations make it possible to strongly evoke the tuberculous origin of the lymphadenopathy. Nevertheless, cytological, histological and/or bacteriological proof, aiming the identification of mycobacterium tuberculosis in the affected lymph node is essential for establishing the diagnosis. However, direct examination, culture and molecular biology are not sensitive. We found in our series a weak contribution of the bacteriology and especially the culture of the BK compared to the other series and the literature. Indeed, the bacteriological study was carried out in 127 cases (46.52%) on FNA liquid and in 96 cases (34.78%) on adenectomy specimen or biopsy of fistulized edges. It was negative in all cases. This could be explained by inadequate conditions of collection, routing and storage of samples. The World Health Organization (WHO) recommends combining identification of the germ by PCR with a standard culture for the antibiogram [13].

Lymph node aspiration cytology is the simplest and most cost-effective first step examination in the event of suspected lymph node tuberculosis, allowing both bacteriological and cytological diagnosis. According to Qian's meta-analysis, the sensitivity of lymph node aspiration biopsy varied from 9% to 90% [5]. In our study, this sensitivity was 72.7%. Cytological diagnosis is based on the demonstration of epithelioid granulomas associated with typical caseous necrosis with or without multinucleated giant cells.

Tuberculosis treatment is a heavy treatment because of the side effects which can reach 14% [14]. A pre-therapeutic assessment is therefore essential, it consists of a blood analysis including: an NFS, a dosage of transaminases because isoniazid and rifampicin are hepatotoxic, a renal function because pyrazinamide and streptomycin are nephrotoxic and uricemia since pyrazinamide is a hyperuricemia drug; an ophthalmological examination including a study of the visual field and color vision because

ethambutol is toxic for the optic nerve which can cause retrobulbar optic neuropathies, but also retinopathies; an audiogram since streptomycin is an ototoxic drug and possibly the acetylation test which makes it possible to identify slow acetylators who present greater hepatic and neurological toxicity towards isoniazid. The rate of slow acetylators varies according to the series from 55% in the study Khelil et al. [15] to 63.8% in that of Touré et al. [16]. In our series, this test was performed in 199 cases (72.1%) and 22% of slow acetylators were found. The acetylation test makes it possible to adapt the dosage of isoniazid in order to avoid hepatic complications.

Antituberculosis drugs exist in combined or dissociated form. For better compliance, it is recommended by the WHO to favor the combined forms to the dissociated forms when possible. The advantage of the dissociated forms is to be able to adapt the doses according to weight, renal function and the acetylation test, or in the event of visual field disorders [17]. In our study, they were prescribed in 43.8% of cases. In the event of adverse effects, contraindications or allergies to a first-line anti-tuberculosis drug, the use of a second-line anti-tuberculosis drug is possible. Minor antituberculosis drugs include levofloxacin, ofloxacin, amoxicillin-clavulanic acid combination, kanamycin, cycloserine, and capreomycin. As for the duration of treatment, the review of the literature does not find any consensus or quality study allowing concluding without controversy on an optimal duration of treatment for lymph node tuberculosis. In Tunisia, the National Program for the Fight against Tuberculosis recommends a treatment of 6 months, including 2 months of quadruple therapy and 4 months of dual therapy. However, Mycobacterium Bovis is naturally not sensitive to pyrazinamide, which makes the first phase of treatment (quadritherapy) insufficient. Some authors therefore recommend, to extend the prescription period for ethambutol from 1 to 4 months to accumulate 3 to 6 months of triple therapy in the event of lymph node tuberculosis leading to suspicion of Mycobacterium Bovis [17]. Several studies have demonstrated the superiority of medical treatment alone compared to surgical treatment. Surgery retains some indications in the event of inconclusive lymph node aspiration cytology, very large lymph node conglomerates sometimes calcified, unfavorable evolution towards fistulization and abscess, or compressive adenopathy [18]. Surgery may also be indicated during treatment in cases of no improvement, drug resistance, paradoxical reaction, or residual adenopathy.

In our study, all patients underwent surgery. In 12 cases (4.34%), the diagnosis was previously confirmed by cytology, but the adenopathy was in a pre-fistulization stage. In 264 cases (95.65%), neither cytology nor bacteriology contributed to the diagnosis.

Follow-up includes clinical, biological, and ultrasound monitoring (in the 2nd month of treatment and at the end) with prompt management of any side effects, emphasizing the importance of adequately educating patients [19]. As with all extra-pulmonary tuberculosis, it is also recommended to schedule follow-up visits at the 12th and 18th month after recovery [20]. Progression under anti-tuberculosis treatment can lead to recovery as it can also be complicated by the occurrence of a paradoxical reaction, resistance to treatment or recurrence. The paradoxical reaction is characterized by adenopathy enlargement, the emergence of new adenopathies, or fistula development, despite receiving appropriate antituberculosis treatment for at least ten days following initial improvement [21]. It is secondary to an intense cellular response due to the presence of tuberculosis antigens. Several therapeutic alternatives are described in the literature, but without any real consensus, such as: surgical excision of adenopathies, iterative punctures with or without local injection of antituberculosis, the addition of corticosteroid therapy or even simply therapeutic abstention with supervision [22]. It was observed in 23 cases (8.3%) in our series in a mean time to of 4 months [2-6 months]. Our approach was surgical in 60.8% of cases. For the other cases, the prolongation of the antituberculosis treatment was sufficient.

Lekhbal's study [23] reported resistance to medical treatment in 12/104 patients and 11 (10.6%) patients benefited from lymph node dissection. Omura [24] adopts the same approach in his study by performing lymph node dissection in 3/38 treatment-resistant patients. In our study, in the absence of an antibiogram, we considered as resistant any pre-existing progressive lymphadenopathy or any appearance of new lymphadenopathy despite a well-conducted 9-month anti-tuberculosis treatment. We identified 41 cases of resistance (14.8%). Our approach was to extend the treatment with cervical lymph node dissection. Recurrence is defined as an increase in the size of a residual lymph node or the appearance of one or more adenopathies after completion of antituberculosis chemotherapy and a phase of clinical remission [25, 26]. The rates vary in the literature from 12% to 23% [23,27]. In our series, we had 2.5% of recurrence cases in a mean time of 8.8 months. Their management was systematically surgical followed by a resumption of antituberculosis antibiotic therapy. However, given the absence of bacteriological diagnosis, it was difficult to distinguish a recurrence from the natural evolution of an infection by an atypical Mycobacterium, the histological aspects of which may be similar.

CONCLUSION:

Lymph node tuberculosis is currently a common pathology in Tunisia. The diagnosis is guided by clinical arguments and complementary examinations.

Due to the low contribution of bacteriology and the high rate of non-contributory cytology, surgery retains an important place in the management of lymph node tuberculosis in association with medical treatment.

Better control of the Tunisian cattle herd and of unpasteurized dairy products would be an essential preventive component in the fight against lymph node tuberculosis.

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