Tuberculous lymphadenitis: Proposal of a protocol

Original Article

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Abstract

Introduction: Tuberculous lymphadenitis (TL) is one of the most common forms of extrapulmonary tuberculosis. It's also the most frequent manifestation in head and neck region.
Objectives: Present cases of cervical TL diagnosed in ENT department of Hospital Garcia de Orta. Propose of a protocol of diagnostic investigation, with focus on excisional biopsy to get material to histological, cultural, and molecular study.
Material and Methods: Retrospective study. Descriptive analysis of cases of TL diagnosed in ENT department of Hospital Garcia de Orta with consultation of clinical records.
Results and Conclusions: This study analyzed 7 cases diagnosed with cervical TL. The patients were mostly female and immunocompetent. The definitive diagnosis was only possible after excisional biopsy of an adenopathy and its histological, cultural and molecular (nucleic acid amplification test PCR) examination. In most cases, the diagnose was only possible with combination of histological and molecular results. The authors propose that in suspected cases, after exclusion of malignancy with CAAF, it should be performed an excisional biopsy with histological, cultural and molecular analyses. This form of actuation will enhance the probability of a correct and prompt diagnosis.
Keywords: Tuberculous lymphadenitis; Early Diagnosis; Polimerase chain reaction; Mycobacterium tuberculosis

Introduction

Tuberculosis, an infectious disease caused by Mycobacterium tuberculosis, is one of the 10 major causes of death worldwide. Until the COVID-19 pandemic, it was the leading cause of death by a single infectious agent, above the immunodeficiency human virus (HIV). Early diagnosis and treatment of this disease are considered key elements in the strategy for its eradication by the World Health Organization (WHO)[1]. In Portugal, its incidence has been decreasing, being below the limit defined as low incidence of

this disease (<20 cases/100,000 people) since 2015[2]. Extrapulmonary tuberculosis (ETB) accounts for 30% of all tuberculosis cases in Portugal[1], with lymph node tuberculosis (LNTB) being one of the most frequent forms of presentation[2]. The indolent and asymptomatic clinical presentation in most cases often hinders and delays diagnosis. Several authors have worked to define the best plan for its investigation by comparing the methods of diagnosis and reporting on the delay in its definition[3,4]. We aimed to analyze the patients diagnosed with cervical LNTB in our department retrospectively to establish a swifter and more effective process of diagnostic investigation.

Materials and Methods

In this retrospective study, the clinical records of patients diagnosed with LNTB in the department of otorhinolaryngology (ORL) of Garcia de Orta Hospital (*Hospital Garcia de Orta - HGO*) were reviewed between January 2017 and December 2021. During this period, seven patients who met at least two of the following diagnostic criteria were diagnosed with the disease: 1) granulomatous lymphadenitis on histological examination; 2) detection of M. tuberculosis by culture; 3) identification of M. tuberculosis by molecular assay (DNA detection by PCR). The following data were collected to characterize the study sample: sex, age, origin, previous or active history of pulmonary tuberculosis, characteristics of the cervical mass, accompanying symptoms, and disease duration. Additionally, an electronic literature search was performed in PubMed using the terms "tuberculous" or "*tuberculosis*," "lymphadenitis" or "lymph node enlargement," "diagnosis," and "clinical pathway" to review and support the proposal for a protocol of action in cases of suspected LNTB.

Results

The clinical data of the seven patients diagnosed with LNTB in the ORL department of the HGO between January 2017 and December 2021 are summarized in Tables 1 and 2. Patients' age varied between 20 and 61 years, and there was a predominance of women (6). The patients were from several countries: Portugal (3), Brazil (2), Angola (1), and Cape Verde (1). The patients did not have a previous or active history of pulmonary tuberculosis, except for one patient who had concomitant HIV-associated immunosuppression. In all cases, the clinical presentation that led to ORL evaluation was the appearance of cervical adenopathies, which, in most patients, were

Table 1
Characteristics of the patients diagnosed with cervical lymph node tuberculosis

C	S	A	Country of origin	History	Lymph node clinical presentation			Accompanying symptoms	Duration of the disease (months)
					Laterality	Pain	Area		
1	F	38	Brazil	Immunocompetent	Bilateral	Painless	II and V	-	3
2	F	33	Brazil	Immunocompetent	Unilateral	Painless	II and V	Weight loss Asthenia	5
3	M	35	Portugal	VIH+; TB pulmonar	Unilateral	Painless	II and V	Night sweats	1
4	F	20	Portugal	Immunocompetent	Unilateral	Painful	IV	Night sweats	1
5	F	61	Cape Verde	Immunocompetent	Unilateral	Painless	II	Asthenia	12
6	F	55	Portugal	Immunocompetent	Unilateral	Painless	IV	-	4
7	F	20	Angola	Immunocompetent	Unilateral	Painless	I and IV	Weight loss Fever	2

Abbreviations: C, case; S, sex; A, age (years); F, female; M, male; TB, tuberculosis; HIV, human immunodeficiency virus.

multiple, unilateral, stony-hard, painless, and involving the cervical regions II, IV, and V. The duration of the disease varied between 2 and 12 months before ORL evaluation. The accompanying symptoms were night sweats, fever, asthenia, and weight loss.

For the investigation of the etiology of the cervical mass, samples were obtained by fine-needle aspiration (FNC) in six cases; the cytology results did not indicate a diagnosis but excluded malignancy. An excisional biopsy of one of the cervical lymph nodes was subsequently performed for histological, culture, and molecular (detection of DNA of M. *tuberculosis*) analysis. The histological findings varied between the chronic inflammatory process without granuloma and necrotizing granulomatous lymphadenitis.

Culture showed mycobacteria of the M. tuberculosis complex in only two cases. The molecular assay for detection of M. tuberculosis DNA was positive in most cases (6). There was no case of resistance to rifampicin and isoniazid. All cases were discussed with the infectious diseases team of the HGO, notified, and referred for treatment to the Almada-Seixal Pulmonology Diagnostic Center (*Centro Diagnóstico Pneumológico - CDP*).

Discussion

Tuberculosis can manifest at several locations of the head and neck region, and cervical LNTB is the most frequent form of presentation. Thus, otorhinolaryngologists should be aware of this differential diagnosis when evaluating a patient presenting with a cervical mass.

Pulmonary *tuberculosis* predominantly affects the male sex. However, several studies have shown that LNTB (form of ETB) is more prevalent in the female sex, which is in line with the results of this study[5]. Owing to the reduction in the incidence and mortality of

Table 2
Summary of the results of the tests performed for investigation of etiology

C	Cytology	AFB testing	Histology	DNA-M-PCR	Culture	Resistance
1	Heterogeneous lymphoid population	-	Necrotizing granulomatous lymphadenitis	+	-	-
2	Nonnecrotizing granulomatous lymphadenitis	-	Necrotizing granulomatous lymphadenitis	+	-	-
3	NP	NP	Chronic inflammatory process, without granulomas	+	-	-
4	Acute suppurative sialoadenitis	-	Necrotizing granulomatous lymphadenitis	+	+	-
5	Necrotizing lymphadenitis	-	Granulomatous lymphadenitis with extensive caseous necrosis	+	-	-
6	Insufficient material	-	Necrotizing granulomatous lymphadenitis	+	NR	-
7	NP	-	Necrotizing granulomatous lymphadenitis	-	+	-

Abbreviations: C, case; +, positive; -, negative; NP, not performed; AFB, acid-fast bacilli (by Ziehl-Neelsen staining); DNA-M-PCR, Detection of DNA of M. tuberculosis by PCR

the disease in Portugal and the similarity between its presentation and more frequent tumors, this diagnosis is often made at a late stage[6]. In this sense, patients originating from countries with a high incidence of TB or contact with family members with suspected TB should raise a suspicion of this disease[6]. In this study, approximately 57% of patients were from countries with a high incidence of TB (Cape Verde: 39 cases/100,000 people; Brazil: 45 cases/100,000 people; Angola: 350 cases/100,000 people)[1].

As described in other studies, the clinical presentation of LNTB usually involves the appearance of unilateral or bilateral, hard, painless, and gradually-growing adenopathies without accompanying constitutional symptoms (in limited cases)[2,5,7].

The diagnostic method in these cases varies among studies. Some authors recommend performing FNC as the first-line diagnostic procedure, while others prefer an excisional biopsy of the cervical lymph node to obtain a sample for histological, culture, and molecular analysis[8,9]. FNC is a simple, rapid, and minimally invasive method used as the initial approach for the study of cervical masses[3]. Cytological analysis can help exclude malignancy and guide the diagnosis. However, samples obtained by FNC are often insufficient for culture analysis to establish a diagnosis of LNTB[10], as was the case in this study. In all cases, it was necessary to perform an excisional biopsy of a cervical lymph node to obtain an adequate sample for further analysis. Moreover, cervical LNTB is frequently associated with paucibacillary forms of the disease, which hinders diagnosis with less representative samples. Therefore, it is often impossible to identify acid-fast bacillus (AFB) with the Ziehl-Neelsen stain, as observed in all cases in this study[4].

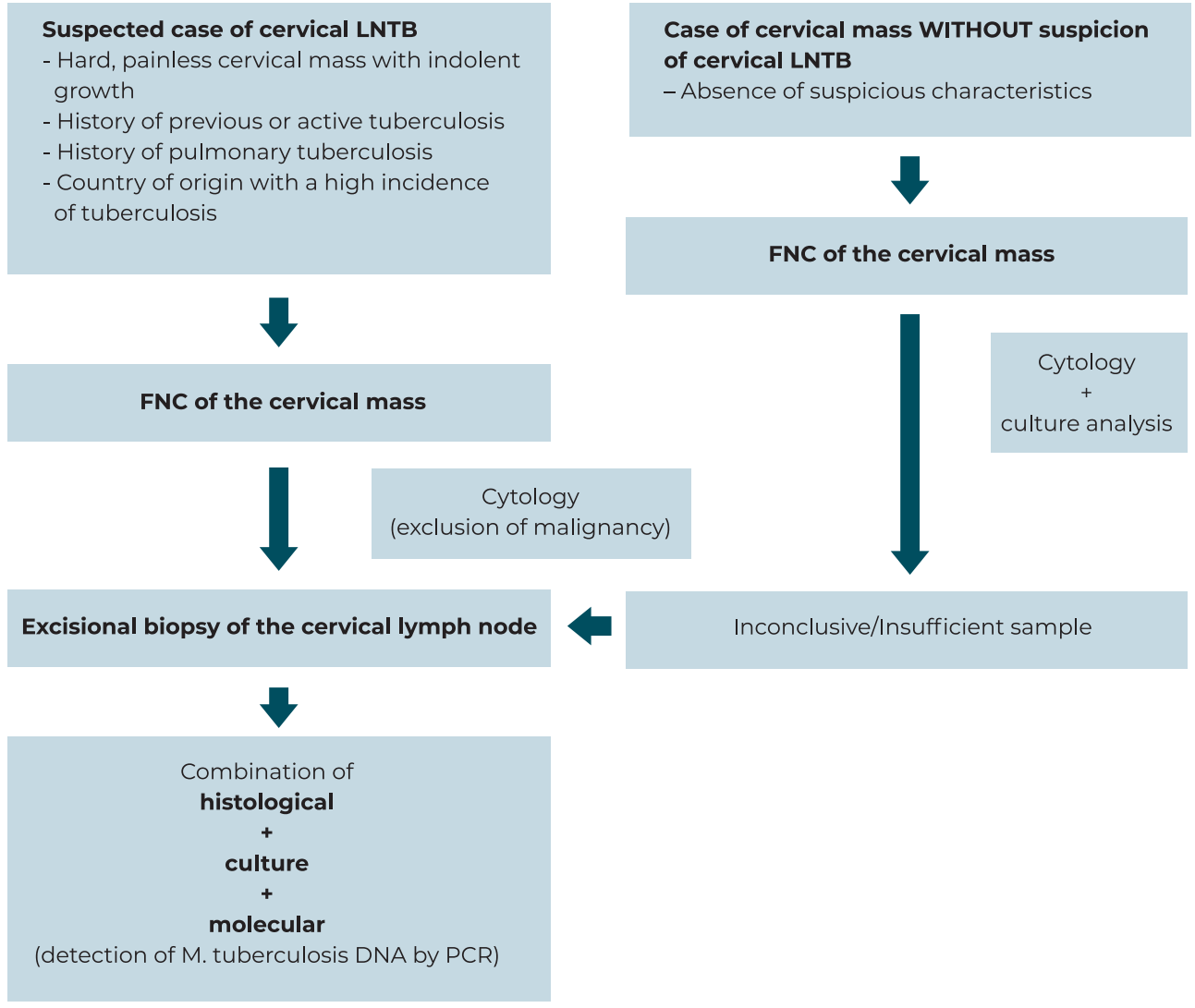
Thus, to ensure a faster diagnosis, in suspected cases of LNTB (patients from countries with a high incidence of TB and/or with contact with an infected individual and/or who are immunosuppressed, with clinical and imaging findings suggestive of LNTB), we recommend performing an excisional biopsy after excluding malignancy through FNC. We believe that with a more representative sample, it is possible to increase the probability and speed of diagnosis confirmation.

The definitive diagnosis is based on the identification of mycobacterium of the M. tuberculosis complex by culture[2]. However, culture analysis has high specificity and low sensitivity; most importantly, the results take a long time (approximately four to six weeks)[3]. This delay in obtaining a result translates into a delay of more than one month for starting the treatment. In this study, the culture was negative in four cases, which is in line with the low sensitivity described in previous studies. These false negative results may be caused by bacilli made non-viable due to sample collection or storage, bacteriostatic substances, paucibacillary forms, aggressive treatment of samples, or the lack of a representative sample. Moreover, although the detection of mycobacteria DNA by PCR is more expensive, this method, which has the fastest results (approximately one week) and higher sensitivity and specificity, allowed the identification of M. tuberculosis in almost all patients in this study.

Considering all the above, we recommend performing an excisional biopsy with histological, culture, and molecular (detection of mycobacteria DNA by PCR) analysis in suspected cases of cervical LNTB after excluding malignancy through FNC. Excisional biopsy, along with a combination of different tests, may ensure timely diagnosis and treatment. Figure 1 shows a flowchart of the procedure used to diagnose this disease.

Although this was a descriptive retrospective study with a small sample, and no statistical analysis was performed to support the proposed recommendation, it highlights the need for further studies to determine a protocol for a swift and efficient diagnosis of LNTB. Additionally, it would be interesting to have future studies with larger samples to analyze the need to perform culture analysis and detection of mycobacteria DNA by PCR

Figure 1
Flowchart of the diagnostic procedure



Abbreviations: LNTB, lymph node tuberculosis; FNC, fine-needle cytology; DNA, deoxyribonucleic acid; M. tuberculosis, Mycobacterium tuberculosis; PCR, polymerase chain reaction.

simultaneously to ensure a definitive and timely diagnosis. Comparing the cost-benefit ratio of this approach with that of the more sensitive test (detection of mycobacteria DNA by PCR) is another interesting objective.

Conclusion

After tuberculous pleuritis, cervical LNTB is the most common presentation of extrapulmonary tuberculous (ETB). Its indolent progression and frequent absence of specific symptoms hinder and delay diagnosis. Patients are often referred to different medical specialties before a definitive diagnosis is made.

Therefore, the definition of procedure protocols and guidelines for investigating suspected cases is essential to ensure rapid diagnosis and, most importantly, timely treatment.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

Bibliographic references

1 - WHO. Global tuberculosis report 2021 [Internet]. Geneva: World Health Organization; 2021. 43 p. Available from: https://www.who.int/publications/i/item/9789240037021

2 - Programa Nacional para a Tuberculose. Manual de Tuberculose e Micobactérias não tuberculosas: recomendações [Internet]. Lisboa: Direção-Geral da Saúde, 2020. Available from: https://www.dgs.pt/documentos-e-publicacoes/manual-de-tuberculose-e-micobacterias-nao-tuberculosas-recomendacoes.aspx

3 – Meghji S, Giddings C. What is the optimal diagnostic pathway in tuberculous lymphadenitis in the face of increasing resistance: cytology or histology?. Am J Otolaryngol. Nov-Dec 2015;36(6):781-5. doi: 10.1016/j.amjoto.2015.08.001.

4 – Mathiasen VD, Hansen AK, Eiset AH, Lillebaek T, Wejse C. Delays in the diagnosis and treatment of tuberculous lymphadenitis in low-incidence countries: a systematic review. Respiration. 2019;97(6):576-584. doi: 10.1159/000499052.

5 – Oishi M, Okamoto S, Teranishi Y, Yokota C, Takano S, Iguchi H. Clinical study of extrapulmonary head and neck tuberculosis: a single-institute 10-year experience. Int Arch Otorhinolaryngol. 2016 Jan;20(1):30-3. doi: 10.1055/s-0035-1565011

6 – Bozan N, Sakin YF, Parlak M, Bozkus F. Suppurative cervical tuberculous lymphadenitis mimicking a metastatic neck mass. J Craniofac Surg. 2016 Sep;27(6):e565-7. doi: 10.1097/SCS.0000000000002870.

7 – Mussedi O, Hameedi A, Al-Dorbie B, Abdullah B. A clinicopathologic review of 21 Cases of head and neck primary tuberculosis. J Oral Maxillofac Surg. 2020 Nov;78(11):1981-1985. doi: 10.1016/j.joms.2020.05.048.

8 – Sivaratnam L, Nawi AM, Manaf MR. An evidence-based clinical pathway for the diagnosis of tuberculous lymphadenitis: A systematic review. Int J Mycobacteriol. Apr-Jun 2020;9(2):107-115. doi: 10.4103/ijmy.ijmy_207_19.

9 – Gautam H, Agrawal SK, Verma SK, Singh UB. Cervical tuberculous lymphadenitis: Clinical profile and diagnostic modalities. Int J Mycobacteriol. Jul-Sep 2018;7(3):212-216. doi: 10.4103/ijmy.ijmy_99_18.

10 – Sellami M, Charfi S, Chaabouni MA, Mrabet S, Charfeddine I, Ayadi L. et al. Fine needle non-aspiration cytology for the diagnosis of cervical lymph node tuberculosis: a single center experience. Braz J Otorhinolaryngol. Sep-Oct 2019;85(5):617-622. doi: 10.1016/j.bjorl.2018.05.009.