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Clinical features of tuberculous lymphadenitis in a low-incidence country

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ABSTRACT

Background: Tuberculous lymphadenitis (TBLA) is the most common extrapulmonary manifestation of tuberculosis (TB) in Denmark. However, the clinical features of patients with TBLA have never been systematically studied in this setting.

Methods: Patients treated for TBLA in Central Region Denmark from 2007 to 2016 were identified using the national TB surveillance register and The Danish Hospital Patient Registry. Data of clinical characteristics and treatment were extracted from hospital records.

Results: Eighty-three TBLA patients were identified. The median age was 32 years (IQR 23–42); 71 (85.5%) were migrants; 58 (69.9%) presented with cervical lymphadenopathy; and 45 (54.2%) had one or more systemic TB symptom such as fever, chills, night sweats, fatigue, and weight loss. Sixty-five patients had no comorbidities (78.3%). HIV co-infection was seen in five (7.2%) of the 69 who were tested for HIV. Abscesses and/or draining sinuses were noted in 13 (15.7%) patients and 15 (18.1%) had concurrent pulmonary infection. The median time from first hospital contact to treatment initiation was 42 days (IQR 16–82) and admitted patients were hospitalised for a median of 7 days (IQR 3–13.5). For 24 patients (28.9%), lymph node material was not sent for mycobacterial culture and 52 (62.7%) had microbiologically confirmed TB. Treatment outcome was successful for 70 patients (84.3%).

Conclusion: In Denmark, TBLA is mainly seen among young and previously healthy migrants presenting with cervical lymphadenopathy and sparse systemic symptoms. The diagnosis is often considerably delayed and not microbiologically verified, implying diagnostic difficulties. Treatment outcome needs to be improved.

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Introduction

One-fourth of the world's population is presumed to be latently infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) (Cohen et al., 2019). The most common extrapulmonary manifestation of tuberculosis (TB) is tuberculous lymphadenitis (TBLA) (Holden

et al., 2019a), which is often attributed to reactivation of latent infection (Fontanilla et al., 2011; Mathiasen et al., 2019a). The diagnosis may be difficult in countries with a low incidence of TB, as the disease is rare, which may delay appropriate treatment (Mathiasen et al., 2019b). TBLA is often located in the cervical lymph nodes, and many benign and malignant conditions mimic the disease (e.g. non-specific hyperplasia, non-TB mycobacteria, sarcoidosis, metastatic carcinomas, and malignant lymphomas), which can be a diagnostic challenge for clinicians who are unfamiliar with this manifestation of TB (Habermann and Steensma, 2000). Systemic symptoms such as fever, fatigue, weight loss, and night sweats are often sparse or absent, and

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the clinical findings are usually indistinguishable from lymphadenitis caused by other conditions (Khan et al., 2009; Morad, 2000).

Patients with prolonged lymphadenopathy, with or without systemic symptoms, and especially patients originating from high-incidence TB areas should be examined for TBLA (Fontanilla et al., 2011). Symptoms caused by perforation to surrounding organs or compression of them may further complicate the diagnosis. Further, in up to 23% of human immunodeficiency virus (HIV)-negative people, treatment response may be slow and new or enlarging lymph nodes may present following treatment initiation (Hawkey et al., 2005; Chahed et al., 2017). This phenomenon, called paradoxical upgrading reaction (PUR), may prompt the physician to consider treatment failure, drug resistance, superinfection, or other diagnoses.

Diagnosis and treatment of TBLA is based on standard TB recommendations, but adjacent corticosteroids may be considered in patients with PUR (Fontanilla et al., 2011). Lymph node material should be obtained by fine-needle aspiration or preferably excisional biopsy, and should subsequently be examined by at least microscopy, polymerase chain reaction (PCR) and culturing. Histological examinations may support the diagnosis together with radiological imaging, tuberculin skin tests or interferon-gamma release assays (IGRAs) (Fontanilla et al., 2011).

In Denmark, TBLA is seen in as many as 15.7% of TB patients annually, most often in young migrants (Mathiasen et al., 2019a). However, the clinical features of these patients have never been systematically studied in this setting. Consequently, this study aimed to evaluate the clinical features of these patients.

Materials and methods

Based on a recent nationwide analysis of TBLA in Denmark, hospital records from all TBLA patients in the Central Region from 2007–2016 were retrieved and analysed (Mathiasen et al., 2019a). The Central Region is one of five regions in Denmark with a population size of approximately 1.2 million, with around 100,000–130,000 migrants, including descendants (Anon, 2020). The demographical and socioeconomical composition of this region is largely similar to other regions in the country.

The cohort was identified using the national TB surveillance register and The Danish Hospital Patient Registry (DNPR) (Schmidt et al., 2015). Patients were included if they were notified with TBLA, including concurrent TB in other sites, to the TB surveillance register during the study period, and/or if they had a relevant International Diseases Classification, Tenth

Edition (ICD-10) discharge diagnosis in DNPR (Figure 1). The Danish Civil Registration Number, a unique personal identifier, was used as observation linkage (Schmidt et al., 2014). The diagnosis of TBLA was defined as either: 1) confirmed (culture-positive or culture-negative but microscopy and PCR positive); 2) probable (culture-negative but microscopy or PCR positive or pathology suggestive of TB); or 3) possible (based solely on clinical assessment) according to the European Centre for Disease Prevention and Control (ECDC) (2020). Treatment outcome was defined according to the World Health Organization (WHO) criteria (Anon, 2015). If patients were not clinically suspected or treated for active TBLA, they were excluded. Patients initially treated and diagnosed in one of the other four regions were also excluded, as well as those with a relevant ICD-10 discharge diagnosis within one year prior to the study period, as this was considered the same episode of TB. Only patients with *M. tuberculosis* complex infection were included (excluding *M. bovis* BCG); patients infected with non-tuberculous mycobacteria were excluded.

Information from electronic hospital records was collected and reviewed using a standardised protocol and manually examined for all patients who were eligible for inclusion. The records contain comprehensive data on demographic factors, symptoms and duration of symptoms, comorbidities and risk factors, TB history, diagnostic procedures, previous and current treatment, treatment outcome, and complications, amongst others. The International Reference Laboratory of Mycobacteriology at Statens Serum Institut, Copenhagen, which serves as a diagnostic facility for the whole country, provided culture, microscopy, PCR, drug-susceptibility, and IGRA results for all patients who had samples sent for examination. Additionally, supplemental regional microbiological, biochemical, histological, and imaging test results were available if performed.

REDCap 7.4 was used for data storage and collection. All statistical tests were conducted using Stata/IC 15.1 (StataCorp, College Station, TX, USA), presented with a two-sided 95% confidence interval and with a significance level of $p < 0.05$, where appropriate. Categorical variables were compared using Fisher's exact test and continuous variables using Wilcoxon rank-sum test. A modified Charlson Comorbidity Index (CCI) score was calculated as a measure of comorbidity based on 19 conditions classified by ICD-8/10 and the diseases were noted if present at the first date of admission (Christensen et al., 2011). The study was conducted in agreement with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Chahed et al., 2017).

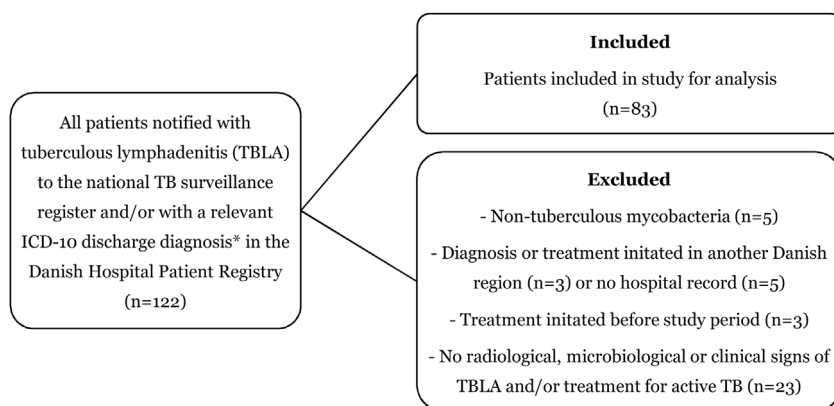


Figure 1. Flow chart of study enrolment of tuberculous lymphadenitis patients in the Central Region Denmark from 2007 through 2016.

Abbreviations: TBLA tuberculous lymphadenitis; TB tuberculosis; ICD-10 International Diseases Classification, Tenth Edition.

*ICD-10 A18.2, A18.3, A15.4, and/or A16.3.

Results

Forty-two males and 41 females were included in the study (Table 1). The median age was 32 years (IQR 23–42). Seventy-one (85%) were migrants or descendants of migrants, and 22 different countries of origin were reported, the five most frequent being: Somalia (*n* = 20), Vietnam (*n* = 10), Philippines (*n* = 6), Thailand (*n* = 4), and Afghanistan (*n* = 3).

Hospital records revealed comorbidities as diabetes mellitus (*n* = 5), HIV infection (*n* = 5), and hepatitis B/C (*n* = 2). No comorbidities were registered for 65 (78.3%) patients and 68 (81.9%) had a CCI score of 0. Sixty-nine (83.1%) were HIV tested, of which five (7.2%) were positive. A history of previous TB was noted in eight (9.6%) and 23 (27.7%) had a presumed or confirmed TB contact. Ethnic Danes were significantly older (median 36.5 years, IQR 29.5–53.5) compared with migrants (median 31 years, IQR 21–39) (*p* = 0.325) but did not significantly differ regarding sex, HIV, previous history of TB, and comorbidities and CCI scores.

Symptoms and clinical findings

Swelling of a lymph node was reported in 56 patients (67.5%) on admission, while other symptoms such as cough and chest pain were less common (Table 1). Systemic symptoms (i.e. fever, chills, night sweats, fatigue, and/or weight loss) were present in 45 (54.2%). The most affected lymph nodes were cervical (*n* = 58, 69.9%) followed by mediastinal (*n* = 27, 32.5%) and intraabdominal (*n* = 14, 16.9%), and 60 patients had lymphadenopathy on one site only (72.3%). Most commonly, the lymph node was present on admission (*n* = 56, 67.5%) with pain or tenderness (*n* = 35, 62.5%). The clinician most frequently described the lymph nodes as unilateral, solitary and soft in consistency (Supplementary A).

Table 1
Patient characteristics.

Patient characteristics	n/N (%)
Females	41/83 (49.4)
Age median, years (IQR)	32 (23–42)
Age group, years	
<15	7/83 (8.4)
15–24	16/83 (19.3)
25–44	43/83 (51.8)
45–64	11/83 (13.3)
>65	6/83 (7.2)
Origin of patients	
Danish	12/83 (14.5)
Migrant*	71/83 (85.5)
History of TB	8/83 (9.6)
One or more concurrent disease site	23/83 (27.7)
HIV status	
Positive	5/83 (6.0)
Negative	64/83 (77.1)
Unknown	14/83 (16.9)
Predisposing factors**	18/83 (21.7)
Charlson Comorbidity Index (CCI) score	
0	68 (81.9)
1–2	10 (12.0)
≥3	5 (6.0)
Symptoms at presentation***	
Fever	24/83 (28.9)
Fatigue	23/83 (27.7)
Unintended weight loss	19/83 (22.9)
Cough	16/83 (19.3)
Night sweats	13/83 (15.7)
Malaise	3/83 (3.6)
Chest pain	3/83 (3.6)

Abbreviations: IQR, interquartile range; TB, tuberculosis; HIV, human immunodeficiency virus.

*Migrants and descendants hereof **Alcohol or drug abuse, captivity (e.g. prison), diabetes mellitus, haemodialysis, steroid treatment or other immunosuppressing therapy, underweight (body mass index <18.5 kg/m²).

Abscesses and/or draining sinuses were noted for 13 patients (15.7%).

Diagnostic features

Confirmed cases were found in 53 patients (62.7%) (Table 2). Among patients with culture-confirmed TBLA (78.0%, *n* = 46/59), 20 (43.5%) and 13 (28.3%) also had a PCR (+/- microscopy) or microscopy positive lymph node sample, respectively. *M. tuberculosis* was the aetiology in 98.1% of all culture-positive samples (*n* = 51/52), while one patient was infected with *M. bovis*. Drug-resistant TB was found in 12.0% of the patients, including two multidrug-resistant (MDR)-TB cases.

Lymph node material was not sent for mycobacterial culture for 24 (28.9%) of the patients and no histological examination was performed for 15 (18.1%). For 13 (15.7%) of the patients, material was obtained using fine-needle aspiration only, while 30 (36.1%) had an excisional biopsy and four (4.8%) had both procedures performed. Other methods included endobronchial ultrasound-guided transbronchial needle aspiration (*n* = 7), swabs (*n* = 9), and/or core biopsies (*n* = 8). Concurrent pulmonary infection was noted in 15 (18.1%) and 60 (72.3%) had isolated TBLA. These findings did not significantly differ between ethnic Danes and migrants.

Of the 27 patients diagnosed with mediastinal TBLA, five had concomitant pulmonary TB and 13 had simultaneous involvement of cervical lymph nodes and the remaining involvement of other

Table 2
Diagnostic findings.

Diagnostic findings	n/N (%)
ECDC case definition*	
Confirmed	52/83 (62.7)
Probable	16/83 (19.3)
Possible	15/83 (18.1)
Microbiology	
Culture-positive lymph node	46/59 (78.0)
Culture-positive in other site	8/47 (17.0)
PCR/microscopy positive sputum	4/44 (9.1)
Drug resistance	10/83 (12.0)
Lymph node pathology suggestive of TB**	55/68 (80.9)
Tuberculin skin test	13/15 (86.7)
IGRA positive	52/56 (92.9)
Chest radiograph at admission	65/83 (78.3)
Temperature median, °C (IQR)***	37.4 (37–38.2)
C-reactive-protein (mg/L)***	
Normal (<20)	40/72 (55.6)
Moderate (20–100)	26/72 (36.1)
High (>100)	6/72 (8.3)
Erythrocyte sedimentation rate (mm/h)***	
Normal (<20)	13/50 (26.0)
Elevated (>20)	37/50 (74.0)
Leukocyte count (10 ⁹ /L)***	
Normal (3.5–9)	59/75 (78.7)
High (>9)	16/75 (21.3)
Haemoglobin (mmol/L)***	
Low (<8)	40/76 (52.6)
Normal (8–10.5)	36/76 (47.4)
Albumin (g/L)***	
Low (<34)	12/68 (17.7)
Normal (34–48)	56/68 (82.4)

Abbreviations: ECDC, European Centre for Disease Prevention and Control; PCR, polymerase chain reaction; TBLA, tuberculous lymphadenitis; IGRA, interferon-gamma-release-assay.

* The diagnosis of TBLA was defined as either 1) confirmed (culture-positive or culture-negative but microscopy and PCR positive), 2) probable (culture-negative but microscopy or PCR positive or pathology suggestive of TB) or 3) possible (based solely on clinical assessment) according to ECDC (European Centre for Disease Prevention and Control (ECDC), 2020).

** Granuloma(s), necrosis, Langerhans giant cells, PCR positive, and/or acid-fast bacilli were considered suggestive of TB.

*** Biochemistry and temperature were not measured in all patients and was only included when conducted within one month of first admission.

organs. Six were diagnosed with isolated mediastinal TB without involvement of other lymph nodes or organs. Four of these were based on clinical assessment, while the two others were bacteriologically diagnosed using material collected using endobronchial ultrasound-guided transbronchial needles. Among the 14 patients with intraabdominal lymph node involvement, eight also had mediastinal gland involvement. Of the remaining six, one had pulmonary TB. Two were diagnosed based on clinical assessment, while three others were bacteriologically diagnosed using material collected with fine-needle aspiration ($n = 3/4$). For the last patient, it was not stated in the electronic patient record what method was used for collecting the sample. Sixty-five (78%) had a chest radiograph conducted within one month of admission. Erythrocyte sedimentation rate was elevated (>20 mm/hr) in 37 (74%) of the patients.

Hospitalisation information and delays

The median duration from onset of symptoms until first hospital contact or admission was 61 days (IQR 28–124) ($n = 72$). The remaining 11 were random imaging findings (i.e. chest radiographs and computed tomography scans taken for other purposes). Acute admission was conducted among 17 (20.2%) patients. The median time from first hospital contact to treatment initiation (health care delay) was 42 days (IQR 16–82) ($n = 83$) and patients were most often seen in one or two departments prior to the one initiating treatment. Patients attended a median of 13 (IQR 9–17) outpatient clinics, excluding patients with relapse or drug-resistant TB and admitted patients were hospitalised for 1–50 days (median 7, IQR 3–13.5). Health care delay did not significantly differ when comparing Danes and migrants.

Treatment and treatment outcome

Fifty-six patients (67.5%) were treated for six months with a standard TB four-drug regimen, while 18 (21.7%) had their treatment prolonged by the clinician, eight (9.6%) stopped medication, and one patient died during treatment due to TB meningitis. Five (6%) of the patients received adjacent

corticosteroids. Treatment outcome was successful for 70 (84.3%), with completed noted for 67 (80.7%) and cured for three (3.6%) (Figure 2). One of these 'cured' patients had concomitant pulmonary TB and was culture-negative in the last month of treatment and on at least one previous occasion. The remaining two did not have concomitant pulmonary TB and should have been classified as completed. Six patients defaulted (7.2%), while the remaining eight (12.0%) were noted as failure ($n = 2$), transferred ($n = 3$), dead ($n = 1$), or unknown ($n = 1$). The two cases of treatment failure were due to MDR-TB. Symptoms consistent with PUR (defined as draining sinuses, enlarging or newly involved lymph nodes) were reported in eight (9.6%) patients within 10 days of treatment initiation. Six of these eight were females, with a median age of 34 years (IQR 32–37), of which five were migrants. Ethnic Danes and migrants did not significantly differ regarding treatment outcome ($p = 0.362$).

Discussion

Patients with TBLA in Denmark were mainly young and previously healthy migrants with affection of the cervical lymph nodes. Systemic symptoms were rarely present. Approximately 60% of the patients were culture-confirmed, while almost one-third did not have material sent for mycobacterial culture. Further, a considerable health care delay was identified, confirming the challenges of diagnosing TBLA. Finally, the treatment success rate was 84.3%. PUR was rare and mainly seen among young migrant females. In accordance with a previous study, the majority of patients were young migrants with the majority being of Somalian origin (Mathiasen et al., 2019a), most likely reflecting the substantial migration from Somalia to Denmark and the enormous burden of TB seen in this population group (Lillebaek et al., 2002). Physicians should be aware of the higher a priori risk of TB, HIV and other communicable diseases in migrants such as refugees and asylum seekers (Alberer et al., 2018; Deen et al., 2018). As previously discussed (Mathiasen et al., 2019a), many of the TBLA cases have unique MIRU-VNTR genotypes and are likely to be reactivation of previously acquired infection, as most TB among migrants in Denmark is estimated to be imported infection

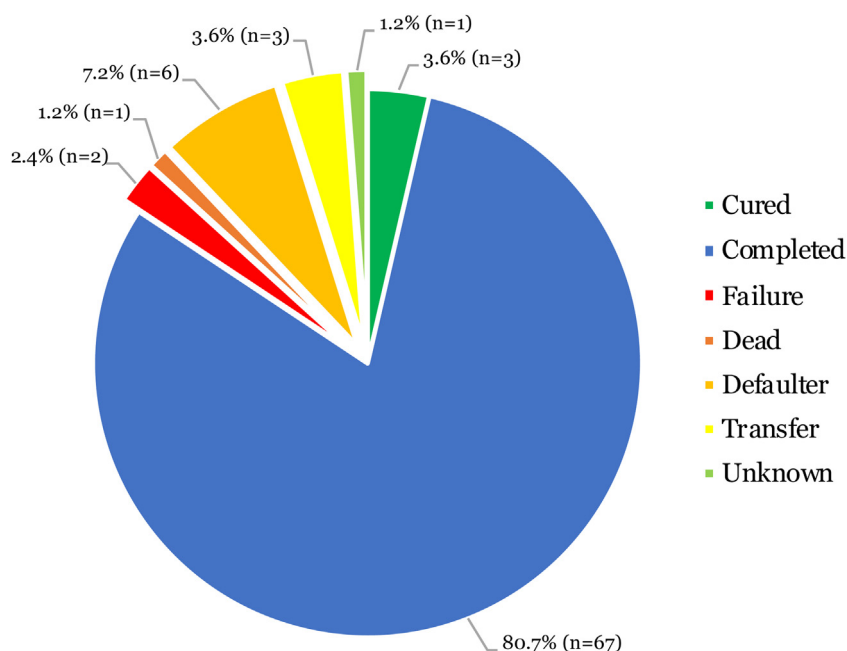


Figure 2. Treatment outcome defined according to the World Health Organization (WHO) criteria (Anon, 2015).

(Lillebaek et al., 2001). Furthermore, as previously observed, a majority of females was not found (Mathiasen et al., 2019a), although gender differences are often highlighted in the literature (Fader et al., 2010; Purohit et al., 2009). TBLA is the most common presentation of extrapulmonary TB (EPTB) in Denmark (Hatleberg et al., 2014; Leutscher et al., 2012; Kristensen et al., 2020; Zhang et al., 2011) and it has previously been reported in up to as many as three-fourths of EPTB cases in the study region, (Leutscher et al., 2012). As discussed by Behr and Waters, an alternative theory is that TB can be viewed as a lymphatic disease with a pulmonary portal of entry, rather than a pulmonary disease, explaining the distinctive involvement of the lymphatic system (Behr and Waters, 2014). Unfortunately, this retrospective study could not prove this theory; thus, it must remain a speculative explanation.

Few patients had comorbidities described in the hospital records, in agreement with notifications from the TB surveillance register (Mathiasen et al., 2019a). However, it was observed that as many as 83.1% were HIV tested compared with the 8% seen in the nationwide study, indicating that notification of HIV could be improved (Mathiasen et al., 2019a). Consistent with the low prevalence of HIV co-infection in Denmark, 7.2% were HIV/TB co-infected (Dragsted et al., 1999). Consequently, few HIV infected people are vulnerable to TB and few are exposed. EPTB is a frequent finding in migrants without any signs of immunosuppression, perhaps as a consequence of late presentation TB. Most migrants are infected prior to arrival in Denmark but reactivate *M. tuberculosis* infection after arrival (Lillebaek et al., 2001). Nonetheless, in almost 20% of the patients, HIV testing was not conducted and it must be emphasized that HIV be ruled out in all patients with TB, due to the close association between these conditions (Shafer et al., 1991).

Comparable with the literature, most patients had unilateral cervical lymphadenopathy, 20% complained of coughing and 54% had one or more systemic symptoms (Fontanilla et al., 2011). The involved lymph node was often affected at admission and most patients had isolated TBLA (72.3%). In a recent nationwide study, it was estimated that almost 90% of TBLA cases presented without concomitant TB in other sites (Mathiasen et al., 2019a), which in the light of these data might be an overestimation due to incomplete notification. Consequently, more may be contagious or have disease at other sites than previously assumed. Three-quarters of the patients had affected cervical nodes, which was similar to many other studies (Fontanilla et al., 2011), highlighting that patients presenting with chronic lymphadenopathy of the neck should be considered for TBLA, especially migrants from high-incidence TB settings. Abscesses and sinuses were seen in up to 16%, which is evidence of a substantial morbidity in these patients.

Culture verification of EPTB has generally been low, due to difficulties in sample collection and the paucibacillary nature of *M. tuberculosis*. Diagnosis was possible in 18% of patients (i.e. solely based on clinical suspicion), while the diagnosis was confirmed in 62.7%. This points out how important it is to carefully collect material, preferably by excisional biopsy, and send it for mycobacterial culture examination (Lau et al., 1990). The gold standard for diagnosing TB remains based on culturing and 43.5% and 28.3% of the culture-confirmed lymph node cases also had a PCR and microscopy positive sample, respectively, establishing the importance of collecting material for culture. Furthermore, routine mycobacterial examination enables physicians to rule-out drug resistance and non-TB mycobacteria (Adzic-Vukicevic et al., 2018). Yet, a considerable number of patients did not have lymph node material sent for mycobacterial culture or histological examination, and it is assumed that the diagnosis of TB is often not considered before late into the course of disease.

Diagnosing TBLA may be challenging, as it involves monitoring the treatment response, PUR may puzzle the clinician, isolates

might be drug-resistant (12%) and lymph nodes biopsies, in comparison with sputum, are not routinely collected at follow-up. Blood sampling may aid the clinician and biomarkers such as C-reactive-protein, erythrocyte sedimentation rate, leukocytes, haemoglobin, and albumin may be useful. An elevated erythrocyte sedimentation rate was seen in 74% of the current cohort. Clinical parameters such as weight gain, improvement of symptoms, and regression of clinical signs may be particularly useful in assessing treatment success in EPTB patients (Jørstad et al., 2019).

As mentioned, it is assumed that the diagnosis of TBLA in Denmark is often delayed and not considered before late into the course of disease. The disease is rare, and a high index of suspicion is required (Mathiasen et al., 2019a; Mathiasen et al., 2019b). This is also supported by the substantial health care delay of a median of 42 days (IQR 16–82), which is comparable to a recent systematic review (Mathiasen et al., 2019b). It is important that all patients with TBLA are screened for pulmonary symptoms and examined with chest radiographs to preclude contagious TB. Twenty-two percent of patients did not have chest radiographs taken within one month of the first admission, potentially delaying the diagnosis of pulmonary TB, but also prolonging the period of contagiousness.

Treatment outcome was successful in 84.3% of patients, which is lower than the overall treatment outcome of extrapulmonary (90.9%) and pulmonary TB (84.1%) in recent reports from 2014 underlying the difficulties in managing this manifestation of TB (Holden et al., 2019a; Holden et al., 2019b). However, the report on EPTB did not include patients with concomitant pulmonary TB.

The main limitation of the study was the retrospective design, as collection of data relied on the individual physicians' completion of hospital records. Consequently, information on lymph node characteristics, TB risk factors, risk of exposure, and comorbidities, among others, was not necessarily presented in the records. In addition, biochemical, microbiological and histological examinations were not systematically performed in all patients. This also demonstrates that the current management of TBLA patients in Denmark is suboptimal (e.g. the incomplete testing for *M. tuberculosis* and HIV). Another limitation was the small number of patients included in the study.

In conclusion, TBLA patients usually present with cervical lymphadenopathy, the diagnosis is often substantially delayed, and half of the patients have systemic symptoms, which is similar to observations in other studies. It is of importance that material is sent for microbiological examination to establish a diagnosis without delay, discover drug resistance and initiate sufficient treatment. This study suggests that TBLA may be a challenging diagnosis and that the clinical management could be improved in this setting.

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Ethical approval

The study was approved by the Danish Data Protection Agency (1–16–02–73–17) and Danish Patient Safety Authority (3–3013–

2108/1). As the study was conducted without any patient contact, approval from The Central Denmark Region Committees on Health Research Ethics was not necessary (1–10-72–189-16). All data presented in public was anonymised (i.e. no single participant or groups were recognisable).

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2020.07.011>.

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