International Journal of Infectious Diseases 78 (2019) 34–38

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Epidemiology and diagnosis of pleural tuberculosis in a low incidence country with high rate of immigrant population: A retrospective study

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ARTICLE INFO

Article history:
Received 3 August 2018
Received in revised form 6 September 2018
Accepted 8 October 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Pleural tuberculosis
Immigrant population
Tuberculosis diagnostic tools

ABSTRACT

Background: The confirmatory diagnosis of pleural tuberculosis (pTB) remains challenging. The aim of this study was to describe the clinical and epidemiological characteristics of pTB patients and assess the yield of different diagnostic procedures in a low burden country with a high rate of immigrant population.
Methods: All adult patients with pTB between 2007 and 2014 were studied retrospectively.
Results: One hundred and three out of 843 patients with tuberculosis had pTB. Fifty-three (54.1%) were male, and the median age was 45 years (range 18–87 years). Fifty-two (50.49%) patients were immigrants. A confirmed diagnosis was reached in 16 patients (15.5%) by microbiological studies of pleural effusion. Lung involvement was demonstrated by sputum smear microscopy in 13/49 (26.5%), sputum GeneXpert MTB/RIF test in 13/20 (65%), and sputum culture in 16/37 (43.2%). High-resolution computed tomography (CT) showed lung involvement in 47.7% of the patients. The cure rate was 91.3% at the 1-year follow-up. Three patients died, all of them within the first month after diagnosis.
Conclusions: The detection of lung involvement increased by two-fold when lung CT was used; this correlated with the likelihood of finding a positive microbiological result on sputum sample testing. Pleural microbiological studies had a low diagnostic yield, and sputum could have a complementary role.

Introduction

Tuberculosis (TB) affects around nine million people and accounts for 1.5 million deaths worldwide every year (World Health Organization, 2014). In countries with a low incidence of TB, the epidemiology and clinical presentation of the disease is changing, with an increasing number of cases of extrapulmonary involvement and a higher proportion of cases in non-native patients (Baussano and Mercadante, 2013). According to the European Union Statistical Agency, 3.4 million immigrants came to the European Union (EU) in 2013, and Spain was in the top five countries receiving immigrants, taking in over 280 000 of them (Migration and migrant population statistics, 2016). Due to this persistent flow of immigrants and the increasing rates expected in the coming years, TB will continue to be a major health issue in the EU (European Centre for Diseases Prevention and Control/WHO Regional Office for Europe, 2013).

After tuberculous lymphadenitis, pleural tuberculosis (pTB) is the most common extrapulmonary presentation of TB disease. pTB can appear as a complication of a primary disease or as a long-term effect of dissemination occurring many years after the initial infection (Davies and Pai, 2007). Factors such as age, chronic diseases, and immunosuppressive conditions have been associated with an increased incidence of pleural involvement (Gopi et al., 2007). The incidence of TB in Barcelona in 2015 was 14.9 cases per 100 000 population, with 10% of pleural involvement (Informeanual, 2015).

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https://doi.org/10.1016/j.ijid.2018.10.005

pTB is a problematic disease due to the difficulty reaching a confirmed bacteriological diagnosis; hence many treatments are started based on a presumed diagnosis (Light, 2010; Richter et al., 1994). The percentage of confirmed diagnosis varies widely (from 12% to 80%) depending on the study location and prevalence of the disease (Porcel et al., 2015; Na, 2014). Although molecular biology methods are being generalized for samples other than sputum, the diagnostic yield of molecular biology studies on pleural effusion is variable and usually lower than that for sputum (Trajman et al., 2014; Porcel et al., 2013).

Pulmonary involvement in pTB has been described in many series, and it is suggested to approach 50% in studies using high-resolution computed tomography (CT) (Kim et al., 2006). Induced sputum or even bronchoscopy may increase the yield of the culture diagnosis of pTB, which is extremely useful in settings with a high burden of resistance to the first-line anti-TB drugs (Conde et al., 2003).

The objective of this study was to describe the clinical and epidemiological characteristics of patients with pTB in a low incidence burden area and establish the yield of the different microbiological techniques.

Materials and methods

Study population

This was a retrospective observational study performed at the Vall d'Hebron University Hospital, a tertiary reference centre included in the International Health Program of the Catalan Health Institute (PROSICS), Barcelona, Spain. Patients older than 18 years of age with a diagnosis of pTB between January 2007 and December 2014 were included. Epidemiological, clinical, and microbiological information was obtained from all patients through a review of the medical records. The diagnostic approach and the treatment were at the discretion of the treating physician.

Pleural tuberculosis definitions

The diagnosis of pTB was classified as bacteriologically confirmed or probable. Bacteriologically confirmed pTB was defined as a positive Ziehl–Neelsen (ZN) smear, positive culture, and/or positive PCR assay from a pleural sample. Probable pTB was considered if a positive response to anti-TB drugs was found and one of the following conditions was present: (1) biochemical diagnosis: pleural exudates with lymphocyte predominance and adenosine deaminase (ADA) level higher than 35 IU/L; (2) histopathological sample showing necrotizing granuloma and/or caseous necrosis; (3) pleural effusion in a patient with confirmed TB at any other location. A positive response to treatment was defined as symptom resolution and pleural effusion improvement by at least 90% of the initial assessment. Pleural biopsy was performed at the discretion of the attending physician. The main reasons for performing a biopsy were a high risk of multidrug-resistant TB, high suspicion of an alternative diagnosis, and a poor clinical course.

Microbiological studies

Pleural samples were examined microscopically using ZN stain. All samples were cultured and incubated in a BACTEC MGIT 960 (Becton Dickinson Diagnostic Systems, Baltimore, MD, USA). Drug susceptibility testing of *Mycobacterium tuberculosis* was done using the BACTEC MGIT 960 SIRE Kit for the first-line drugs: streptomycin, isoniazid, rifampicin, ethambutol, and pyrazinamide (Kent and Kubica, 1985). When resistance to any first-line drug was detected, the drug susceptibility test was broadened to the following antibiotics: amikacin, capreomycin, streptomycin, ethionamide, moxifloxacin, and ofloxacin. Molecular biology testing was done with the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) on pleural samples.

Imaging assessment

A chest X-ray was performed for all patients. The need for a high-resolution CT scan was at the discretion of the treating physician. Lung parenchyma findings suggestive of TB, such as nodules, infiltration, cavities, and pleural thickening, were recorded.

Statistical analysis

Categorical variables are presented as the absolute number and proportion, and continuous variables are expressed as the median and range. The Chi-square test or Fisher's exact test was used to compare the distribution of categorical variables, as appropriate, and the Mann–Whitney *U*-test or Student *t*-test was used to assess continuous variables (following evaluation for a normal distribution through the Kolmogorov–Smirnov test). Results were considered statistically significant if the two-tailed *p*-value was <0.05. IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

Ethical considerations

The study protocol was approved by the Institutional Review Board of Vall d'Hebron University Hospital (Barcelona, Spain). An exemption from obtaining informed consent was granted. Procedures were performed in accordance with the ethical standards laid down in the Declaration of Helsinki as revised in 2012 in Fortaleza, Brazil (World Medical Association, 2016).

Results

Of an overall 843 patients with TB, a total of 103 patients fulfilled the inclusion criteria for pTB. The median age of the study population was 45 years (range 18–87 years) and 51.4% were male. Twenty (19.4%) of the patients had an immunosuppressant condition, including seven patients with an HIV infection. More data regarding patient characteristics and epidemiological information are shown in Table 1. Figure 1 depicts the number of total TB and pTB cases per year.

Regarding symptoms, the chief complaints were fever ($n = 83$, 80.5%), pleuritic chest pain ($n = 70$, 67.9%), cough ($n = 56$, 54.3%), general weakness ($n = 41$, 39.8%), dyspnoea ($n = 39$, 37.8%), diaphoresis ($n = 37$, 35.9%), and weight loss ($n = 33$, 33.9%). The median duration of symptoms was 21 days (range 3–365 days). Four patients (3.8%) had a personal history of previous TB (two pulmonary TB and two pTB). More clinical and epidemiological information is detailed in Table 2.

When analyzing the biochemical characteristics of the pleural effusion, 14 of 97 cases (14.4%) did not have a lymphocytic predominance in pleural effusion and five of 101 cases (4.95%) had an ADA concentration below the suggested limit to consider the diagnosis. All of these cases had a confirmed TB diagnosis by culture or a pleural biopsy showing granulomas. Table 3 shows the diagnostic yield according to biochemical characteristics of the pleural effusion.

A confirmed diagnosis was made in 16 (15.5%) patients: 14 by microbiological studies of pleural effusion and six by microbiological studies of pleural biopsy, four of them with negative pleural effusion microbiological studies. The diagnosis for 87 patients

Table 1
Demographic characteristics of the patients ($N = 103$).

Variable	Number (%)
Sex (male)	53 (51.5%)
Age (years), median (range)	45 (18–87)
Foreign born	52 (51.5%)
Latin America	20 (38.4%)
Africa	14 (26.9%)
Asia	11 (21.2%)
Eastern Europe	7 (13.4%)
Duration of stay in Spain prior to diagnosis (years), median (range)	3 (0–25)
Immunosuppressive conditions	20 (19.4%)
HIV infection	7 (6.7%)
Autoimmune diseases	4 (3.9%)
Steroid therapy	4 (3.9%)
Anti-TNF inhibitor therapy	2 (1.9%)
Liver transplantation	1 (0.9%)
Kidney replacement therapy	1 (0.9%)

TNF, tumour necrosis factor.

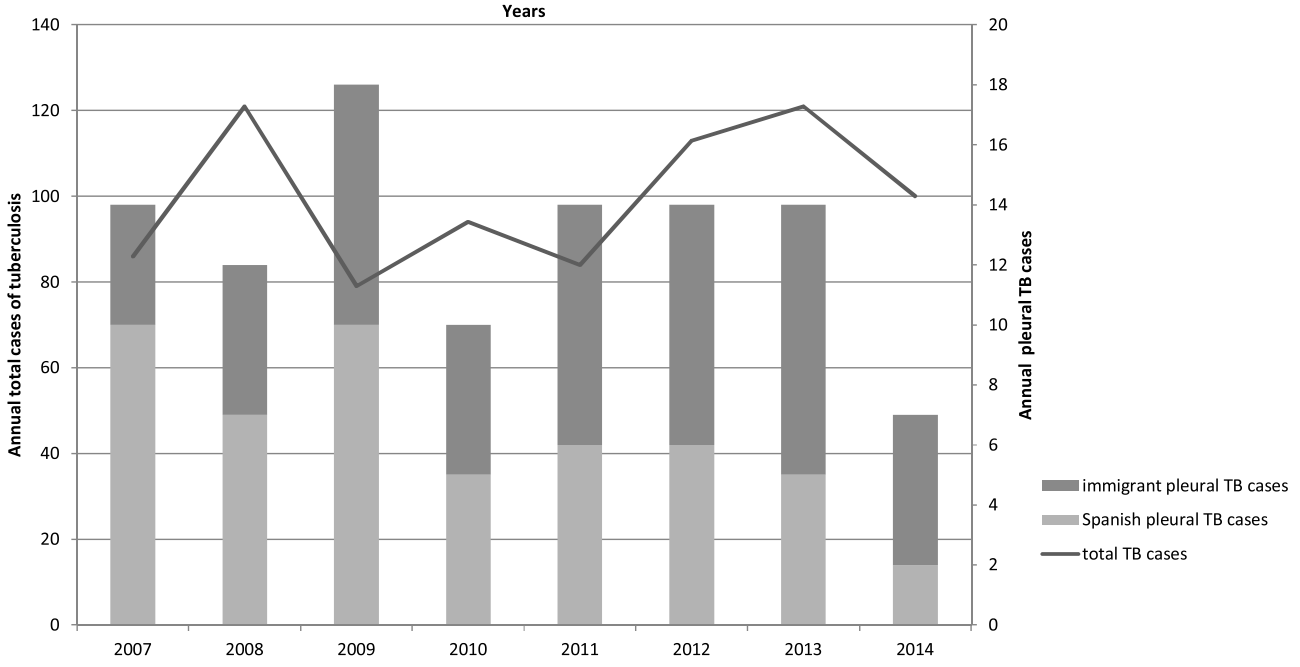

Figure 1. Number of pleural TB and total cases of TB at Vall d'Hebron University Hospital. Barcelona, Spain 2007–2014.

(84.5%) was probable TB. Regarding the accuracy of diagnostic techniques, the yield was superior in sputum and pleural biopsy samples than in pleural effusion (Table 4).

Twenty-four (23.3%) patients had lung involvement as seen on chest X-ray. High-resolution CT was done for 57 (55.34%) patients. Twenty-seven out of 57 (47.4%) showed lung involvement on high-resolution CT scan, with 16 patients having any tomographic finding of tuberculous lung involvement not visualized in the X-ray, thereby increasing the diagnostic yield of having lung compromise by 2.3 times. Moreover, patients with lung compromise had a higher yield on diagnosis in the sputum sample, compared with those who did not have lung compromise (72.2% vs. 25%; $p = 0.002$).

In the drug susceptibility test assessment, no resistance to anti-TB drugs was found. Thirty-nine (37.8%) patients developed any adverse effect related to the anti-TB drugs. The most frequent were nausea ($n = 8$, 7.7%), mild hepatic cytolysis ($n = 7$, 6.7%), and cholestasis ($n = 5$, 4.8%).

The great majority of therapy regimens (96%) included the standard four-drug treatment including isoniazid, rifampicin, pyrazinamide, and ethambutol. Only four patients were treated with a fluoroquinolone during follow-up, with side effects being the cause of the switch in all cases. The median duration of the treatment was 6 months (confidence interval interquartile range 5.5–8.5 months).

After 1 year of follow-up, 94 (91.3%) patients were cured, five were lost to follow-up, and four had died. Three of the deaths occurred in the hospital within the first month after the diagnosis. In brief, one patient suffered a haemophagocytic syndrome associated to the TB, another patient had multifactorial encephalopathy (age, renal replacement therapy, TB infection, and anti-TB treatment) that led to death, and one cirrhotic patient developed a fulminant hepato-renal syndrome concomitant with the TB infection. The remaining patient died of reasons unrelated to TB during follow-up. There was no case of relapse during the study period.

Table 2
Epidemiological and clinical data of patients with pleural TB (2007–2014)[a].

	Overall	Spanish ($n=51$)	Immigrant ($n=52$)	p-Value
Sex, male	53 (51.4%)	26 (50.9%)	27 (51.9%)	0.92
Age (years)	45 (18–87)	46.9 (18–87)	34.3 (18–77)	<0.001
Time to consultation (days)	21 (3–365)	28 (4–365)	20 (3–180)	0.31
Extrapleural involvement	31 (30%)	25 (49%)	24 (46.2%)	0.85
HIV co-infection	7 (6.7%)	5 (9.8%)	2 (3.8%)	0.27
Immunosuppression[b]	10 (9.7%)	6 (11.7%)	4 (7.6%)	0.52
Positive TST	45 (83.3%)	19 (73.1%)	26 (96.3%)	
Empiric anti-TB treatment	87 (84.4%)	42 (82.3%)	45 (86.5%)	0.37
Confirmed pleural TB	16 (15.5%)	9 (17.6%)	7 (13.5%)	0.55
Pleural biopsy	17 (16.5%)	10 (19.6%)	7 (13.4%)	0.28

TB, tuberculosis; TST, tuberculin skin test.
[a] Data are presented as the number (percentage) or the median (range).
[b] Immunosuppression includes autoimmune diseases and/or immunosuppressant agents, corticoid therapy, biological therapy, and transplantation.

Table 3
Proportion of diagnosis according to characteristics of the pleural effusion.

Samples/methods	Total	Confirmed	Probable	p-Value
ADA-positive[a] in pleural effusion	96/101 (95%)	14/16 (87.5%)	82/85 (96.5%)	0.177
Pleural exudates	98/100 (98%)	15/16 (93.8%)	83/84 (98.8%)	0.296
Lymphocytic pleural effusion	83/97 (85.6%)	11/16 (68.8%)	72/81 (88.9%)	0.052
ADA-positive[a] + lymphocytic effusion + pleural exudate	77/96 (80.2%)	10/16 (62.5%)	67/80 (83.8%)	0.081

ADA, adenosine deaminase.
[a] ADA > 35 IU/IU/L.

Table 4
Diagnostic accuracy of the different techniques employed.

	Pleural effusion			Sputum			Pleural biopsy
	Ziehl–Neelsen	Culture	PCR	Ziehl–Neelsen	Culture	PCR	Any diagnostic finding
Total	2/79	10/60	8/52	13/49	16/37	13/20	4/17[a] 7/17[b]
Diagnostic accuracy	2.5%	16.6%	15.38%	26.5%	43.2%	65%	23.53%[a] 41.2%[b]

[a] Positive smear, positive culture, or positive molecular biology test.
[b] Granuloma or caseous necrosis.

Discussion

In this study, the clinical and epidemiological characteristics of pTB in a tertiary hospital of a low burden country, over eight consecutive years, are described. In Vall d'Hebron University Hospital, pTB accounts for 12.2% of the total number of TB cases. Of note, half of the cohort was foreign-born, mainly from Latin America and Africa (in concordance with the immigrant population in Barcelona). The pTB diagnosis was mainly based on clinical information, biochemical characteristics of the pleural effusion, and microbiological results obtained for another location, with only 22 (21.3%) having a microbiological confirmatory result from a pleural sample. Sputum samples showed a good yield, especially in patients with lung involvement found on imaging.

From a clinical perspective, these patients were mostly young adults, with no important co-morbid predisposing conditions, and with the classical signs and symptoms of fever, pleuritic chest pain, and cough. The duration of symptoms varied from 3 days to 1 year.

The yield of biochemical pleural effusion characteristics was high, with an exudative effusion being the most common finding. In a recent study of 548 cases performed by Sahn et al. (2013) the diagnosis had 100% specificity if the pleural effusion met the following criteria: protein >5 g/dl, lymphocyte count > 80%, and ADA > 45 mg/dl IU/L (sensitivity of 35%). In the patients included in the present study, considering protein > 3.5 g/dl, lymphocyte predominance > 50%, and ADA > 35 mg/dl, IU/L the three conditions were present in 80.2% (77/96 cases).

The yield of PCR on pleural effusion was lower (seven positive cases out of 51, 13.7%) than that observed for PCR on sputum (13 positive cases out of 20, 65%). According to other publications, the sensitivity of the GeneXpert assay on pleural effusion is usually low (around 25%), with high specificity (around 95%) (Lusiba et al., 2014). The reasons for this are not clear, but could probably be attributed to the presence of PCR inhibitors in pleural fluid and a low bacillary load (Du et al., 2015).

Regarding pleural biopsy, despite being considered the most useful technique to confirm a suspected diagnosis, with rates of positivity between 60% and 95%, the indication for this in pTB is not clear (Kirsch et al., 1997). Performing a pleural biopsy is not without risks, although direct injury to the adjacent organs (liver, kidneys, spleen) is very rare. The incidence of pneumothorax with a closed needle is variable and depends on the operator, but could be between 8% and 18% (Gouda et al., 2006). In the present study, pleural biopsy was performed at the discretion of the attending physician and the yield was 64.7% (11/17 cases). The procedure was performed in selected patients, in whom the diagnosis was not reached with other procedures. For this reason, the different yields of the diagnostic techniques should be interpreted with caution.

Interestingly, in this study, the sputum yield remained high even in the absence of involvement seen on chest X-ray. In a previous report Conde et al. (2003), found a yield in induced

sputum of 55% in a cohort of Brazilian patients with presumptive pTB and no apparent lung involvement on chest X-ray; thus sputum induction in patients with pleural effusion provides an invaluable opportunity to confirm a probable diagnosis and to perform a susceptibility study to guide treatment.

From our perspective, we consider it justified to start anti-TB treatment in the case of an immigrant from a high incidence TB country presenting with a febrile process accompanied by an exudative pleural effusion with a high number of lymphocytes and a high ADA level, unless there is a high risk of multidrug-resistant TB or an alternative diagnosis is highly probable. In this situation, a pleural biopsy should be considered. In fact, the diagnosis was probable in 87 (84.5%) patients in the study cohort and treatment was started on this assumption, leading to a 100% therapeutic response.

In the study cohort, the prognosis of the disease was favourable in the majority of patients and the cure rate was >90%, which is in concordance with the global plan to end TB (the STOP TB programme) (The paradigm Shift, 2015). The deaths that occurred were not associated with the pleural involvement itself and were related to multi-organ compromise, co-morbid conditions, and immunosuppression. In other series, as in this study, mortality has usually been associated with advanced age and co-morbid conditions not related to TB (Efsen et al., 2014).

The limitations of this study include those inherent to the retrospective design. It should be noted that there was variability among physician criteria and a lack of molecular biology tests at the beginning of the study period. Moreover, pTB is a disease that is challenging to confirm with a difficult-to-establish gold standard diagnosis, hindering the assessment of diagnostic methods.

In conclusion, pTB represents 12% of all TB diagnoses at Vall d'Hebron University Hospital, with half of the cases diagnosed in immigrant patients. A confirmed diagnosis was achieved in 21.3% of cases using pleural samples. The detection of lung involvement increases by two-fold when lung CT is used, which correlated with the likelihood of finding a positive microbiological result in the sputum sample. Pleural microbiological studies had low diagnostic yield, and sputum samples, even in the absence of X-ray abnormalities, may support the diagnosis and provide information on drug susceptibility of the bacillus.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to individual privacy reasons, but are available from the corresponding author on reasonable request.

Funding

The authors declare that they received no funding for the study.

Conflict of interest

The authors declare that they have no competing interests.

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