Routine examination for tuberculosis is still indicated during bronchoscopy for pulmonary infiltrates

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ABSTRACT

INTRODUCTION: Tuberculosis (TB) can present in numerous ways and can be radiological indistinguishable from cancer. In several guidelines for bronchoscopy (FOB) in low-incidence areas, a *Mycobacterium tuberculosis* test is only recommended when TB is clinically suspected. Due to the expenses associated with *M. tuberculosis* cultures, we did an analysis of tests obtained by FOB and other invasive procedures (endoscopic ultrasound (EUS)-guided needle biopsy via the oesophagus or trachea and percutaneous needle lung biopsy (PNLB)).

METHODS: All patients tested positive for *M. tuberculosis* by culture and with samples obtained by FOB, EUS or PNLB in the 2008-2012 period were identified retrospectively in two centres in a low-incidence area (Copenhagen, Denmark). Patient records and radiological reports were reviewed.

RESULTS: A total of 57 (1.2%) patients out of the 4,680 tested were *M. tuberculosis* culture positive. Of the 57 patients, 40.3% (n = 23) presented with isolated upper lobe infiltrates and 29.8% (17) with cavitating infiltrates. Isolated chest lymphadenopathy was seen in 8.8% (n = 5)[2]. In 33.3% (n = 19) of the patients, radiography was not typical of TB (not upper lobe, no cavity, not isolated lympadenopathy, not miliary). Of the 57 patients, 48 were diagnosed by FOB, six by EUS and three by PNLB. *M. tuberculosis* samples were taken in an estimated 34% of all procedures.

CONCLUSION: *M. tuberculosis* culturing should always be considered when performing FOB in patients with lung infiltrates of unknown origin, even in a low-incidence country as Denmark. EUS and PNLB should also be considered when sampling material.

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Tuberculosis (TB) is an infective disease caused by *Mycobacterium tuberculosis*. Denmark has a low incidence of TB at 6.8/100,000 [1], although the incidence is 17/100,000 in Copenhagen, the area of the present study. Nearly 50% of the TB cases in Denmark are found among immigrants from high-TB-burden countries. TB infections are most frequently located to the lungs, but any organs can be affected. When pulmonary TB is suspected, three sputum samples are recommended [2]. These samples should be analysed by smear and culture, whereas polymerase chain reaction (PCR) is optional [2]. If the patient is unable to produce expectorate, samples can be obtained by gastric washing or flexible bronchoscopy (FOB). TB can present clinically in numerous ways, and can be radiologically indistinguishable from cancer [3]. FOB is an useful procedure for obtaining diagnostic material directly from lung infiltrates [4, 5]. FOB is indicated for patients presenting with haemoptysis, radiological abnormalities of unknown origin (i.e. suspicion of malignancy, interstitial lung diseases or infection of unknown aetiology, including TB) or chronic cough.

Mycobacteria are detected by smear microscopy as acid-fast bacilli (AFB). The sensitivity of this test on sputum is 60%. Mycobacterial culture has a higher sensitivity than other detection methods and is regarded the gold standard for detection of *M. tuberculosis.* Culture allows species identification as well as susceptibility testing and epidemiological strain typing, but takes 3-8 weeks. PCR for *M. tuberculosis* complex can detect *M. tuberculosis* rapidly, but the overall sensitivity of PCR on sputum compared to culture is typically around 85% [6].

Contrary to lung cancer, TB is easy and inexpensive to cure, and even a few missed cases will be unacceptable and have a huge impact on the disability-adjusted life years. Furthermore, by identifying and treating TB patients and performing case finding, the risk of TB transmission is reduced [2].

In the two bronchoscopy centres in this study, sampling for mycobacteriological diagnostics has not been routine, but done at the discretion of the individual physician.

Earlier studies (**Table 1**) from countries with a high or intermediate TB prevalence have found several unexpected TB cases by bronchoscopy, and therefore recommend that samples are obtained routinely for microscopy and culture [7-9]. However, studies from the US and Israel, countries with a low TB incidence, do not recommend routine culture [10-14]. Shitrit et al found that none tested positive to TB among 125 patients who underwent FOB due to atelectasis, pulmonary mass or haemoptysis with a normal chest X-ray [13].

The British Thoracic Society is only recommending routine culture and smear microscopy of immunocompromised patients with pneumonia and patients from areas with a high or intermediate TB prevalence.

ORIGINAL ARTICLE

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TABLE 1

Bronchoscopy and tuberculosis studies.

Reference	Country	TB incidence	Method	Patients, n	Patients with TB, n (%)
Kvale et al, 1979 [10]	USA	Low	Culture	859	3 (0.35)
Jett et al, 1981 [11]	USA	Low	Microscopy Culture	4,120	32 (0.77)
Shitrit et al, 2005 [13]	Israel	Low	Microscopy Culture	300	4 (1.33)
Shitrit et al, 2005 [12]	Israel	Low	Microscopy Culture	168	1 (0.6)
Sarkar et al, 1982 [7]	India	High	Microscopy Culture	164	15 (9.1)
Kim et al, 2007 [8]	Korea	Intermediate	Microscopy Culture	733	47 (6.4)
Ip et al, 1989 [9]	Hong Kong	High	Culture	1,734	144 (8.3)
Talker et al, 2013 [14]	Israel	Low	Microscopy Culture	362	2 (0.55)
Mohan & Sharma, 2008 [15]	Taiwan	High	Culture	1,024	38 (3.71)
Rubins & Bofenkamp, 1999 [16]	USA	Low	Culture	436	0 NTM: 73 (17)

NTM = nontuberculous mycobacteria; TB = tuberculosis.

TABLE 2

Patient characteristics

Mean age, yrs	52.9
Male, %	64.9
Never smokers, %	28.1
Pack-years, n, mean	25.8
Diabetes, %	12.3
Systemic corticosteroid therapy, %	0.0
Inhalation corticosteroid therapy, %	8.8
HIV, %	0.0
Intra-venous drug abuse, %	3.5
Alcohol abuse, %	35.1
Former TB infection, %	5.3
Known TB exposure, %	12.3
Weight loss, %	42.1

TB = tuberculosis.

On this background, we decided to investigate the diagnostic yield of *M. tuberculosis* testing material obtained by FOB, endoscopic ultrasound (EUS) and percutaneous needle lung biopsy (PNLB) in consecutive patients mostly presenting with lung infiltrates. Furthermore, we describe the characteristics of the patients who tested positive.

METHODS

Patients in the Capital Region of Denmark (population 1.7 million) who are suspected of pulmonary malignancy are admitted to Gentofte and Bispebjerg Hospitals.

All patients with a positive *M. tuberculosis* culture, PCR or microscopy obtained by FOB, EUS or PNLB from these two hospitals in the course of a five-year period (from 1 January 2008 to 31 December 2012) were included in the study. The patients were identified in the database of Statens Serum Institut. Patient files and radiology reports were reviewed retrospectively.

Ethical considerations

Since this was a retrospective study, approval from the local Research Ethics Committee was not required. The study was approved by the Danish Data Protection Agency (ID: 02358-GEH-2013-024).

Trial registration: not relevant.

RESULTS

A total of 57 patients (37 males, 20 females; aged 24-80 years) with culture-positive samples obtained by FOB, EUS or PNLB were identified. Of these, 48 were endobronchial samples (bronchial lavage, bronchoalveolar lavage or brush biopsy), six were obtained by EUS and there were PNLBs. In the study period, 4,680 samples were tested for TB (4,568 endobronchial and 112 biopsies) giving a total positive rate of 1.2%. In the studied period, an estimated 13,400 procedures were performed at the two hospitals, meaning that TB samples were taken in approximately 34% of the cases.

Microscopies were positive for AFB in 27% (15/56) and PCR were positive in 82% (18/22) of the *M. tuberculosis* culture-positive samples.

A total of 53% (30/57) of the TB-positive patients were born in Denmark or Sweden, 19% (11/57) were from Greenland and 28% (16/57) were from one of the following countries: Afghanistan, Ghana, India, the former Yugoslavia, China, Morocco, Pakistan, Rumania or Somalia. The background information is summarised in **Table 2**.

In 26% (13/57) of the cases, the physician had no suspicion of TB based on the patient's history, symptoms and available radiology.

Isolated chest lymphadenopathy was seen in 8.8% (5/57), 56% (32/57) showed isolated parenchymal infiltrates and 35% (20/57) had both lymphadenopathy and parenchymal infiltrates.

In all, 40% (23/57) presented with isolated upper lobe infiltrates and 30% (17/57) with cavitating infiltrates. ?21% (12/57) had pleural effusion. None of the patients had a normal computed tomography (CT) of the chest.

In 33% (19/57) of the patients, radiography was not typical of TB (not upper lobe, no cavity, not isolated lymphadenopathy, not miliary).

No microscopy or PCR samples were found to be falsely positive. In the five-year period, 36 patients were

found with nontuberculous mycobacteria by FOB/EUS/PNLB.

DISCUSSION

In the present study of the value of using invasive procedures in the detection of lung TB in a low-TB-burden country, we examined the characteristics of the patients who were diagnosed with TB by culture. *M. tuberculosis* was detected in 1.2% of the patients, which is similar to other studies from non-endemic areas (Table 1).

Interestingly, one third of the patients presented with a chest radiography non-suggestive of TB, and in 26% of the cases TB was not initially suspected. These patients would not have been tested according to most recommendations. The majority of the patients were ethnic Danes and were not immunocompromised. Therefore, our study suggests that testing for TB should be considered in all patients undergoing bronchoscopy as a part of the assessment of non-specific thoracic pathology. In accordance with Shitrit et al [13], we fund no TB patients with a normal chest X-ray or CT. Furthermore, the majority of our study population was male, one third had alcohol abuse and approximately 40% had unintentional weight loss. No patients were treated for TB based on falsely positive samples.

A decision analysis conducted by Mohan & Sharma [15] concluded that early use of FOB is the best approach in patients suspected of sputum smear-negative pulmonary TB. Our study shows that endosonography and percutaneous lung biopsy should also be considered when sampling material for testing.

Several hospitals perform routine cultures of bronchoscopic samples for mycobacteria, even in non-endemic areas. As far as we know, only ten studies written in English have addressed the routine bronchoscopic *M. tuberculosis* culture (Table 1).

Some of the first studies that evaluated routine testing of *M. tuberculosis* by FOB showed low prevalence of TB. Both studies were conducted in the United States and showed prevalence rates between 0.35% [10] to 0.77% [11], Table 1. This was later confirmed by Shitrit et al [13] who evaluated routine culture of FOB samples for mycobacteria in a non-endemic area. The study showed a low prevalence of TB from bronchial washings (1.33%). All these results are similar to those presented in a recent prospective study by Talker et al [14]. They evaluated 362 patients with pulmonary diseases from a non-endemic area. The patients underwent FOB with routine culture for *M. tuberculosis* and only two cases (0.5%) of active TB were found. Rubins & Bofenkamp [16] investigated the role of routine cultures for TB during bronchoscopy in 436 patients from a non-endemic area. None were found to have active TB. A total of 17% of the cases were found with NTM.

Samples incubated in Löwenstein-Jensen medium.

Studies from intermediate and high endemic areas reported prevalence rates between 6% and 9% [7-9]. The authors suggested that all patients from high endemic areas should be tested for TB routinely. As regards the non-endemic areas, only immunocompromised patients with pulmonary masses should undergo routine TB culture [12].

In our setting, a significant number of the patients (34%) were tested for TB by culture even though it was not compulsory. This suggests that the physicians have chosen to take the samples based on a relatively low suspicion of TB.

The present study includes almost as many patients as the previous ten studies together. However, it is a limitation that the study was performed retrospectively in selected patients. Furthermore, in tertiary hospitals like ours, a greater incidence of TB in the patients admitted may be expected. Therefore, it is difficult to draw general conclusions from the study. However, our results show that 26% of the diagnosed TB cases would have been missed if diagnostic material for TB were only obtained in patients with a clinical and radiological suspicion of TB.

The current price of TB microscopy and culture is 726 DKK (97 euro) per sample. This corresponds to an approximate total annual cost of 1,900,000 DKK (260,000 euro) in our two hospitals if all patients were tested.

Whenever an invasive procedure, especially FOB, is performed, the physician should consider examining for TB, even in a low-incidence country. The expenses are relatively limited and the benefits are high compared to diagnosing and treating patients with lung cancer. A TB patient is usually cured after six months of treatment, and transmission is prevented.

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