Indications, diagnostic yields and complications of transbronchial biopsy over 5 years in the State of Qatar

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ABSTRACT

Objectives: To review the indications, diagnostic yields and complications of transbronchial biopsy (TBB) in a tertiary hospital in the State of Qatar.

Methods: A retrospective review of our records revealed 1006 adult flexible fibre optic bronchoscopies (FFB) at Hamad General Hospital, State of Qatar between January 1999 and December 2003. A total of 85 (8.4%) TBB were performed, but complete data were available for 71/85 (83.5%), which were reviewed for indications, diagnostic yields and complications.

Results: Adequate samples were obtained in 58/71 TBBs (81.7%), while 13/71 TBBs (18.3%) yielded bronchial mucosa. The main indications in 16/71 (22.5%) TBBs for radiographic localized pulmonary disease were to rule out tuberculosis (TB) in 13 cases, and malignancy in 3 cases. Tuberculosis was verified in 3 (23%) of the 13 cases with localized disease. Fifty-five out of 71 (77.5%) TBBs were performed for radiographic diffuse pulmonary disease: 16/55 (29%) for miliary shadows, while 39/55 (70.9%) were carried out for reticular/reticulonodular infiltrates. Histopathology showed granulomatous lesions consistent with TB in 10/16 (62.5%) cases of miliary shadow. In the other pattern of diffuse disease, the histopathological diagnosis were obtained in 25/39 (64%) cases. It showed non-specific pulmonary fibrosis in 13 cases, sarcoidosis in 4 cases, connective tissue disease associated interstitial fibrosis in 4 cases, bronchiolitis obliterans organizing pneumonia (BOOP) in one case, eosinophilic pneumonia in one case, amiodarone toxicity in one case and lymphangitis carcinomatosis in one case. The main complications were minor bleeding <50 cc in 17 cases (23.9%), pneumothorax in 7 cases (9.8%)) and one case had sepsis.

Conclusion: Our experience substantiates previous reports of the value and safety of transbronchial biopsy in the rapid diagnosis of smear-negative miliary TB. In diffuse lung diseases of a non-infectious nature, other than sarcoidosis, lymphangitis carcinomatosis and few other conditions, a pathological diagnosis are much less likely to be reliably made on small pieces of tissue such as those provided by TBB.

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Transbronchial biopsy is a safe and useful investigation in the diagnosis of diffuse or localized pulmonary disease. Often, the initial procedure of choice especially when sarcoidosis, lymphangitis carcinomatosis, eosinophilic pneumonia, Goodpasture's syndrome or infections such as tuberculosis (TB) are suspected.[1,2] However, interstitial lung diseases pathology frequently are non-homogeneous and difficult to characterize definitely on the basis of small transbronchial biopsies. In this study, we reviewed retrospectively the indications, diagnostic yields and

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complications of transbronchial biopsy (TBB) carried out in a tertiary hospital, which has the main bronchoscopy unit in the State of Qatar.

Methods. In 5 years (January 1999 to December 2003), a total of 1006 adult TBB were carried out at Hamad General Hospital; the only referral hospital in Qatar. Transbronchial biopsies were performed in 85 (8.4%) cases, but the complete records of 71/85 (83.5%) cases were available for review. Thirty-five (49%) patients were referred from in-patient departments, 4 (6%) patients from intensive care unit, and 32 (45%) patients from out-patient departments. Each fibreoptic bronchoscopies (FFB) report was completed by the attending physician which includes indication, anesthesia, findings, and complications. All patients had a chest radiograph, complete blood count, and a coagulation profile. In suspected cases of TB, 3 samples of sputum were negative for acid fast bacilli (AFB) by direct smear. Pulmonary function tests, computerized tomography (CT) scan of the chest or specific blood tests were carried out depending on the clinical situation. A written consent was obtained from the patient or relatives.

The procedure was carried out under continuous monitoring of electrocardiogram, pulse rate, blood pressure and oxygen saturation. Pre-medications were used in 32/71 (45%) cases. Topical Lidocaine was used as a local anesthetic and oxygen was given continuously through nasal prongs sufficient to maintain adequate saturation as measured by pulse oximetry. The transnasal route was used for the introduction of the scope, while the endotracheal route was used in the 4 intubated ICU cases. The Olympus FFB and the Vujinon video-scopes were used. All the procedures were carried out according to the international recommendations.

Bronchoalveolar lavage (BAL), bronchial washes and a total of 3-5 TBBs were taken from all cases. These samples were then processed in the microbiology and pathology laboratories. Transbronchial biopsies were performed under fluoroscopic guidance in 19 (26.7%) cases, while they were unguided in 52 (73.2%) cases. The bronchoscope was wedged in the desired segment and maintained in that position throughout the biopsy. The biopsy forceps was then passed through the suction channel and extended to the lung periphery. Once the forceps was in the proper position, the patient was asked to exhale completely. As the patient exhales, the forceps was advanced 1-2 cm in an open position, closed and then removed from the bronchoscope to obtain the specimen. This procedure was repeated 3-5 times to obtain adequate samples. The patient was observed for 2 hours following the procedure for possible complications and evaluation by a chest x-ray.

Results. ***Indications.*** Complete data were available for 71 cases (42 males and 29 females), with an average age of 44 years (SD ±14.7 years), and an age range of 18-85 years. They were divided into those with radiographic localized disease and those with radiographic diffuse disease. Those with diffuse disease had miliary shadow or reticular/reticulonodular infiltrates. The different diagnostic indications, number of adequate biopsies, diagnostic yields by TBB and final diagnosis reached in all cases either by TBBs or other clinical means are shown in **Table 1**.

The major diagnostic indications in localized disease were for suspected TB in 13 cases and malignancy in 3 cases. Tuberculosis was the final diagnosis in 6 of 13 cases, 3 of them by documentation of granulomatous lesions in TBBs, 2 of the 3 cases had positive microbiology by BAL for AFB, while one case had granulomatous lesion in histopathology but had a negative microbiology. One case was positive for TB with microbiology only, while 2 cases had cavitary lesions and showed therapeutic response to anti-tuberculous treatment. Only one of the 3 cases suspected of malignancy was diagnosed by TBB, while CT guided FNA had diagnosed the other 2 cases. Of 55 (77.5%) TBBs carried out for diffuse pulmonary infiltrates, 16 (29%) cases were for suspected TB due to miliary shadow in the chest x-ray while having negative smear. Thirty-nine (70.9%) cases were for reticular/reticulonodular infiltrates with a suspicion of pulmonary fibrosis in 18 cases, sarcoidosis in 7

Table 1 - Different diagnostic indications, adequate biopsies (adequate Bx), diagnosis by biopsy (Dx by Bx), diagnostic yields (Dx), and final diagnosis (final Dx).

Pulmonary infiltrate	N	Adequate Bx	Dx by Bx	Final Dx
Localized infiltrate				
Tuberculosis	13	10	3	6
Malignancy	3	3	1	3
Total	**16**	**13**	**4**	**9**
Diffuse pulmonary infiltrate				
Miliary shadow	16	15	10	16
Reticular/ Reticulonodular				
Sarcoidosis	7	6	4	7
Eosinophilic pneumonia	3	2	1	3
BOOP	1	1	1	1
Pulmonary fibrosis	18	13	13	18
CTD	5	4	4	5
Lymphangitis	3	2	1	2
Amiodarone toxicity	1	1	1	1
Multiple nodules	1	1	0	0
Total	**39**	**15**	**25**	**16**

BOOP - bronchiolitis obliterans organizing pneumonia,
CTD - connective tissue disease

cases, connective tissue disorders (CTD) in 5 cases, eosinophilic pneumonia in 3 cases, lymphangitis in 3 cases, pneumonia in 2 cases, bronchiolitis obliterans organizing pneumonia (BOOP) in one case, multiple pulmonary nodule in one case and amiodarone toxicity in one case.

Adequate biopsies were taken in 15 out of 16 (93.7%) cases with miliary shadows. Ten of the 16 (62.5%) cases showed granulomatous lesions suggestive of TB. Of the 6 cases with non-diagnostic TBBs, 3 had positive microbiological studies from either BAL or bronchial wash, while 3 showed therapeutic response. One case of granulomatous infiltrate initially treated for TB was later diagnosed as sarcoidosis. Thirty of the 39 (76.9%) cases with diffuse reticular/reticulonodular infiltrates had adequate biopsies. Non-specific pulmonary fibrosis was diagnosed in 13 cases, sarcoidosis in 4 cases, CTD-related interstitial fibrosis in 4 cases, eosinophilic pneumonia in one case, lymphangitis carcinomatosis associated with breast cancer in one case and the diagnosis was excluded in the other case, BOOP in one case and drug toxicity due to amiodarone in one case. In one case of multiple pulmonary nodules, adequate biopsy was not diagnostic.

Complications. There were no fatalities associated with TBBs. Complications were divided into minor (bleeding of <50cc and a pneumothorax that is treated conservatively) and major (bleeding of >50cc and a pneumothorax that needed chest tube insertion). Minor bleeding occurred in 17 of the 71 (23.9%) cases which were controlled with adrenaline, and one case showed moderate bleeding exceeding 100cc. Pneumothorax occurred in 7 of the 71 (9.8%) cases and chest tube insertion was needed in 4 of them. It was not related to whether fluoroscopy was used or not, as 2 of 19 cases with fluoroscopy assisted TBBs had a major pneumothorax that needed chest tube insertion, and 5 pneumothoraces occurred in 49 cases after unguided procedures. We had one case of post-procedure septicemia that needed admission to the hospital. In that case, the bronchial wash, BAL and the blood culture grew *Klebsiella pneumonia.*

Discussion. Transbronchial biopsy is an important diagnostic technique in pulmonary medicine, especially when infectious causes, sarcoidosis, lymphangitis carcinomatosis, eosinophilic pneumonia, Goodpasture's syndrome are suspected.[1,2] Transbronchial biopsy has also taken a role in diagnosing solitary pulmonary nodule.[3] Unfortunately, pathological diagnosis in diffuse lung diseases of a non-infectious nature, other then sarcoidosis,[4] and lymphangitis carcinomatosis,[5] and few other conditions are much less likely to be reliably made on small pieces of tissue such as those provided by TBB. Frequently, the histopathological reports on such samples describe non-specific changes that could represent the end stage of innumerable inflammatory processes or at best may report changes that are "consistent with" whatever diagnosis the clinician was considering rather than being "diagnostic" of a given pathology.[6]

The low number of TBBs performed in our institute is related to many factors. First, TB with miliary infiltrate is mostly diagnosed by microbiological studies of the BAL and bronchial wash without the need for TBB. Secondly, although interstitial lung diseases (ILD) of different etiologies are commonly seen in our center, but patients tend to present with advanced pulmonary fibrosis, with a consequent but expected low diagnostic yield from the TBB. Thirdly, many patients with diffuse ILD are reluctant to undergo TBB or may have contraindications such as pulmonary hypertension. As a result many of our patients with diffuse ILD undergo bronchoscopy without TBB.

Microbiological studies with BAL/bronchial washes may be enough for the diagnosis of TB (the main indication for bronchoscopy in localized pulmonary disease in our center) but, 13 cases with localized pulmonary disease had TBBs to rule out TB. One case showed caseating granuloma consistent with TB but with negative microbiological studies, while 2 cases were histopathologically and microbiologically positive. Another case was diagnosed by microbiological studies only. This might support the need to have TBB whenever possible aid in the diagnosis of pulmonary TB.

One of the 3 cases in localized pulmonary infiltrate had malignancy. Transbronchial biopsy or transbronchial needle aspirations are not a common diagnostic test performed in our center for pulmonary nodules or peripheral pulmonary infiltrate; those cases are usually referred for CT guided FNA.

In smear negative miliary TB, bronchoscopy with BAL, brushing, and TBB have been shown to be useful. In combined data from 2 series, an immediate diagnosis (positive smear or pathology) was made at bronchoscopy in 65% of patients.[7,8] If the chest radiograph does not show potential pulmonary involvement, bronchoscopy would be expected to be a less useful diagnostic modality.

In our study of smear negative miliary pulmonary infiltrate, TBB was a diagnostic tool of help in diagnosing 10 (62.5%) of the 16 cases. It was the only diagnostic test in 7 (43.7%) cases, while microbiological studies provided a diagnosis in 6

(37.5%) cases given a total yield of 13 (81.2%) cases when combining TBBs and microbiological studies (**Table 1**). Microbiological studies were the only diagnostic test in 3 (18.7%) of the 16 cases. In this study, histopathology had a higher diagnostic yield than microbiology, while the combined results of histopathology and microbiology increase the chance of detecting TB in miliary pulmonary infiltrate. The presenting symptoms in the 16 cases with military infiltrate were: cough in 13 (81.2%), fever in 9 (56%), loss of weight in 7(44%), and shortness of breath in 4 (25%). Tuberculin tests were positive in 8 (50%), and 9 (56%) had elevated erythrocyte sedimentation rate (ESR).

Transbronchial biopsy is the recommended procedure in most cases of sarcoidosis. Its diagnostic yield depends largely on the experience of the operator, ranging from 40% to more than 90% when 4-5 lung biopsies were carried out.[9] Four of our 7 cases (57%) demonstrated non-caseating granuloma consistent with sarcoidosis. The remaining 3 cases were diagnosed based on other clinical or histopathological diagnosis.

In this study, pulmonary fibrosis diagnosed on many cases of ILD, but they tended to be non-specific except for the group of sarcoidosis, eosinophilia pneumonia, lymphangitis and BOOP (**Table 1**). Cases of ILD associated with CTD were scleroderma in one case, systemic lupus erythematosus in one case and rheumatoid arthritis in 3 cases. Interestingly, ILD was the initial presentation leading to the diagnosis of rheumatoid arthritis in 2 cases, and the case diagnosed initially as BOOP, later developed full blown picture of rheumatoid arthritis thus demonstrating the importance of investigating for the underlying CTD whenever a patient presents with ILD.

The use of TBB in diffuse ILD is also an area of variable practice. While a number of ILDs can be adequately identified via TBB, many require larger samples of tissue. Although TBB are not helpful in making the diagnosis of idiopathic pulmonary fibrosis (IPF).[10,11] Many clinicians believe TBBs may be acceptable in the diagnosis of some processes that may mimic IPF.[12,13] Inspite of the abnormal finding in many cases, however they do not confirm IPF, instead they exclude it by identifying an alternative specific diagnosis in the right clinical setting or with the use of special histopathological methods or stains for example, malignancy, infections, sarcoidosis, hypersensitivity pneumonitis, BOOP, eosinophilic pneumonia, or pulmonary histiocytosis. In addition, TBB should not be used to assess the degree of fibrosis or inflammation, due to the small sample size (2-5 mm). Open or video-assisted thoracoscopic surgical lung biopsy is performed in a minority of patients with chronic ILDs, likely reflecting the pessimism that findings on lung biopsy will alter the proposed treatment plan.[14] A review of 200 patients with IPF in the United Kingdom showed that transbronchial or open lung biopsies were performed in only 33% and 7.5% of patients; the diagnosis of IPF was made on clinical grounds in most cases.[13] Clinical practice in the United States and other countries often mirrors this approach of relying largely on clinical and radiological features to make the diagnosis of IPF.[15,16] In most clinical series describing patients with presumed IPF, open or thoracoscopic lung biopsies were performed only in a minority of patients and many of these reports included patients with CTD or occupational exposures known to be associated with the development of ILD. The TBB yield in idiopathic interstitial pneumonias (IIPs) proved to be low, except for diffuse alveolar pneumonia/acute interstitial pneumonia, and occasionally organizing pneumonia/chronic organizing pneumonia. But, the primary role of TBB is to exclude sarcoidosis and certain infections. Bronchoalveolar lavage is not always required in the assessment of the IIPs.[17] The major complication in our study was pneumothorax. We have relatively a higher rate of pneumothorax in 7 cases (9.8%) with 4 needed chest tube insertion. Pue et al[18] reported 4% of pneumothorax. Pneumothorax was not related to whether the procedure was guided by fluoroscopy or not. In some studies[19] the use of radiographical screening for performing TBB was associated with a lower likelihood of pneumothorax requiring chest tube drainage while others have reported the safety of unguided transbronchial biopsy.[20,21] Minor bleeding of <50 cc occurred in 17 cases and only one case had moderate pulmonary hemorrhage exceeding 50 cc. One of our cases of TBBs had septicemia after bronchoscopy and both the bronchial secretions and the blood culture grew *Klebsiella pneumonia*. Fever is commonly reported following bronchoscopy, but bacteremia is either not reported,[22] or reported at a rate of 2.9% and 6.5%.[23,24] Bronchoscopy has been associated with the development of new pulmonary infiltrate[25] and on occasions with the development of fatal pneumonia.[25,26]

In conclusion, this retrospective review of TBBs in our center over 5 years substantiates the previous reports of the value and safety of TBB in the rapid diagnosis of smear-negative miliary TB. Pathological diagnosis in diffuse lung diseases of a non-infectious nature, other than sarcoidosis, lymphangitis carcinomatosis and few other conditions, are much less likely to be reliably made on small pieces of tissue such as those provided by TBB.

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