Closed percutaneous pleural biopsy

A lost art in the new era

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ABSTRACT

الأهداف: تقييم العلاقة بين حجم وعدد الخزعات البلورية، وتأثيرها على التوصل للتشخيص النهائي لأمراض الغشاء البلوري عامة والالتهاب الدرني خاصة .

الطريقة: مئة وثلاثة وأربعون مريض كان لديهم التهاب بالغشاء البلوري تم تحويلهم إلى قسم الأمراض الصدرية – مستشفى مبارك الكبير – الكويت، خلال الفترة مابين يناير 1999م وحتى ديسمبر 2007م. كان لدى جميع المرضى زيادة في بروتين السائل البلوري وزيادة في عدد كريات الدم البيضاء (Lymphocytes)، حيث تم أخذ خزعات بلورية للتوصل إلى التشخيص. تم تحليل نتائج الفحص السريري والنتائج المخبرية للخزعات (عدد وحجم الخزعات).

النتائج: تم التوصل إلى التشخيص المرضي من خلال الخزعة البلورية في 52% من الحالات. حجم الخزعة (3mm) أو أكثر، عددها (4≥) كانت مرتبطة وبشكل ملحوظ مع نتائج التشخيص حالات التهاب الدرني (p=0.007 – p=0.047) .

خاتمة: إن الحصول على أربع خزعات بلورية أو أكثر، وخزعات البلورية بحجم (3mm) أو أكبر، والمزيد من أجل الفحص المجهري للأنسجة يؤدي إلى نتائج ايجابية أكثر في تشخيص الالتهاب الدرني للغشاء البلوري.

Objectives: To assess the association between size and number of biopsy specimens obtained by percutaneous closed pleural biopsy, with overall diagnostic yield in general, and histopathological evidence of tuberculosis pleurisy, in particular.

Methods: One hundred and forty-three patients, with a high index of clinically having tuberculous pleurisy, were referred to the respiratory division of Mubarak Al-Kabeer Hospital in Kuwait during a 9-year period (January 1999 to December 2007). All subjects with exudative lymphocytic predominant effusion underwent percutaneous closed pleural biopsy, looking for tuberculous granulomas. The clinical diagnosis and pathological characteristics (number and size of biopsy samples) were analyzed.

Results: Overall diagnostic yield of percutaneous closed pleural biopsy in all cases was noticed to be 52%. The larger biopsy sample size of 3 mm and more, and the higher number of specimens (≥4) were significantly associated with an increased diagnostic yield for tuberculous pleurisy (p=0.007 and 0.047).

Conclusions: Obtaining 4 or more biopsy samples, and larger specimens of 3mm and more for histopathological evaluation, through percutaneous pleural biopsy, results in a better diagnostic yield for tuberculous pleurisy.

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Pleural effusion is the most common pleural condition faced by physicians. It carries a wide differential diagnosis that needs to be worked up properly. The most challenging are the unilateral exudative effusions. In this regard, percutaneous pleural biopsy has evolved over the years as a diagnostic tool for such effusions.[1,2] The technique of pleural biopsy was first described by De Frances[3] in 1955. Since then, it has undergone modifications and improvements to

the current most commonly used needles: Abram[4] and Cope.[5] Diagnostically, there is no significant difference between the 2 techniques, yet Abram's needle tends to obtain larger samples.[6] Pleural biopsy is recommended as the first invasive diagnostic procedure provided the clinical, radiological, and biochemical analysis of the fluid prove to be exudative and suspicious for tuberculosis (TB) or malignancy.[7] The diagnostic accuracy of blind pleural biopsy for TB has been variable in different series, ranging from 60-95%.[8,9] It is unfortunately lower for malignant effusions.[10,11] In many centers, chest physicians are shying away from closed pleural biopsy due to the emergence of medical thoracoscopy, which requires further training, more expensive equipment, and is time-consuming, and hence, probably not affordable in many countries. We examined the role of Abram's needle in clinical practice in the evaluation of lymphocytic exudative pleural effusion. The diagnostic accuracy, number of biopsies required, and sizes of acquired biopsy are assessed in this study. Our objectives of the study were: first, to determine the diagnostic yield of closed pleural biopsy out of total cases, and second, to find any association between the total number of biopsy samples obtained, and the size of largest sample for individual patient with the diagnostic yield, in general, and histopathological evidence of TB pleurisy, in particular.

Methods. During a 9-year period (January 1999 to December 2007), 143 patients with lymphocytic predominant exudative effusion, based on Light's criteria,[12] were referred to the respiratory division of Mubarak Al-Kabeer hospital in Kuwait, for further evaluation. The clinical index of suspicion for TB pleurisy was high among all subjects given the high prevalence of TB in Kuwait. Since thoracoscopic pleural biopsy, whether medical or surgical, is not readily available in our institution, all patients were advised to undergo percutaneous closed pleural biopsy for confirming clinically suspected TB pleurisy, through histopathological evidence of tuberculous granulomas. Approval from the ethics committee of the hospital was obtained. Written consent was taken, and patients were fully informed of the procedure's risks. The procedure was performed, under completely aseptic technique, using standard Abram's needle by an experienced respirologist. The number and size of biopsies obtained were variable, depending on patient's tolerance, and co-morbid illnesses. The samples were fixed immediately in formalin solution and delivered to the pathology department, for sample measurements by a technician under the pathologist's supervision on the same day. Two pathologists examined each sample. All samples were sent to the pathology department immediately, where total number of pleural specimens, and size of largest sample (mm) for each patient, were recorded. The site of pleural effusion, whether right or left was also recorded.

In our study, a "definitive diagnosis" was defined as: histopathological evidence of granuloma (**Figure 1**) plus either favorable clinical and radiological response to anti-TB treatment, or a positive Ziehl-Neelsen (ZN) stain in biopsy sample. Alternatively, the pathology report may also indicate a totally different definitive diagnosis such as, malignancy, since many of its clinical features may simulate tuberculosis.

Statistical analysis. The data on demographic characteristics; age, gender, and ethnicity, and clinical findings, such as, number and size of biopsy samples, were recorded from the patients' records and their histopathology reports. The total number of pleural samples for each patient was subcategorized to <4 and ≥4 samples. Also, the size of largest pleural specimen for each subject was grouped in <3 and ≥3 mm. Statistical analysis was performed using the Statistical Package for Social Sciences, SPSS PC version 16.0 (SPSS Inc., Chicago, IL., USA). Chi-square or Fisher's exact test was applied to establish any association between number and size of biopsy samples with diagnostic yields in general, and of TB pleurisy in particular. A 2 tailed *p*-value of <0.05 was considered statistically significant.

Results. The study sample was categorized into 4 ethnic groups: Kuwaitis, Middle Easterns, Indian subcontinent, and South East Asians (**Table 1**). Kuwaiti nationals were separated from the Middle Eastern group for statistical and socio-economic reasons. Of these, the largest group was patients from the Indian subcontinent,

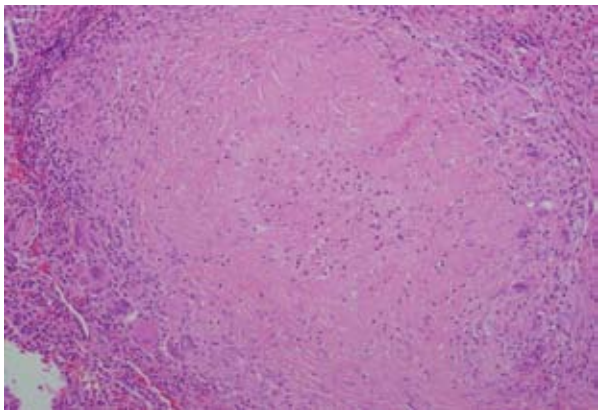

Figure 1 - Typical caseating epithelioid granuloma.

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while the least were from South East Asia. The overall mean age was 41.0±15.5 years, slightly higher in males (41.8±15.6) than females (39.3±15.5). The mean age of Arabs (Kuwaitis and Middle Eastern) was significantly higher as compared to Asians, both from the Indian Subcontinent and South East Asians. Male gender dominated the study group accounting for two-thirds of the total population. Males dominated throughout the study groups, except South East Asians, where the male to female ratio was 1-3. Right-sided pleural effusion was slightly more common of the total cases, than those with left-sided effusion. In assessing the diagnostic yield of percutaneous pleural biopsy, approximately 74 (52%) patients had a definitive diagnosis, of whom 66 (46%) showed definitive granulomas (caseating or non-caseating) in their samples. Sixty-two (94%) out of the 66 cases had a sample size of ≥3 mm, and 52 (79%) had ≥4 samples. These individuals were started promptly on anti tuberculosis therapy with subsequent clinical and radiological improvement on follow up (**Figure 2**). Only 4 cases had positive ZN stain, and all 4 had granuloma on biopsy. The remaining 8 (6%) subjects with a "definitive diagnosis" had malignancy and, hence, were referred to the oncologist. Approximately two-thirds (66.7%) of patients, who had definitive tuberculous pleurisy, were Indian ethnicity (**Figure 3**). **Table 2** shows the correlation between the overall diagnostic yield and TB pleurisy cases among all biopsies on one hand, with the number, and size of pleural samples per subject on the other hand. The overall definitive diagnostic yield, in general, and TB pleurisy, in particular, becomes statistically significant when 4 or more (≥4) samples per patient were obtained by percutaneous pleural biopsy. Similarly, the likelihood of a definitive diagnosis and TB pleurisy of all biopsies significantly increased when the size of largest pleural sample obtained per patient was 3 mm and more. Furthermore, when examining all biopsy proven cases of TB pleuritis, the proportion of those with 4 samples and more (≥4), and those with size of 3 mm and above (≥3 mm) increases significantly to 78.8% and 93.9%, among TB pleurisy patients (**Figure 4**).

Discussion. In the new era, through the advent of new diagnostic techniques having an excellent diagnostic accuracy, percutaneous closed pleural biopsy is losing its lust as a valuable diagnostic tool in the evaluation of undiagnosed exudative pleural effusions. Many physicians tend to shy away from this cheap procedure, given the rapid availability of thoracoscopy and other highly sophisticated biochemical tests, especially in developed countries. In Kuwait and other developing countries, where TB prevalence is high, percutaneous closed pleural biopsy remains a favorable, cheap, and safe diagnostic tool for undiagnosed lymphocytic effusions, such as TB pleurisy, a post primary TB phenomenon, with granulomatous inflammation of the affected pleura occurring in adults from endemic areas. Unfortunately, Adenosine Deaminase (ADA) analysis of pleural fluid was not available in our institution at the time of the study.In Kuwait, the prevalence of tuberculosis is relatively high, according to the WHO, accounting for 25 cases per 100,000 of population.[13] Thus, in our study, the presence of granulomas in the pleural samples (whether caseating or non-caseating) was considered diagnostic of TB pleuritis in clinically suspected individuals. This was confirmed with a definitive favorable clinical and radiological response to anti TB therapy on follow up. A positive ZN stain of the pleural specimens is another confirmatory test. The results showed that more than half of the study population had a definitive diagnosis, which is comparable to other studies.[8,10,14] The TB pleuritis was evident in 46% of all cases, with malignancy constituting the remaining 6%. This is a fairly good diagnostic yield of a simple, and safe test, sparing the patient a more invasive and expensive diagnostic procedure such as thoracoscopy; whether medical or surgical, with its consequences including possible lengthier hospital stay. The ZN stain of the pleural samples was positive in only 4 cases (3%) of the sample, all of whom had granulomas on histopathological examination. This accounts for nearly 6% of biopsy proven cases.

Of the 4 population subgroups, TB was found to be the most prevalent among the Indian subcontinent group, accounting for 66.7% of the total biopsy proven TB pleurisy cases with granulomatous pleuritis. This is significant due to the presence of a large Indian population size of 44%, combined with the fact that the prevalence of tuberculosis among this group

Table 1 - Demographic characteristics of patients with exudative effusion suspected of tuberculosis pleurisy (N=143).

Ethnic group	n (%)	Mean age (years)	Gender		Site of effusion	
			Male	Female	Right	Left
Kuwaiti	39 (27.3)	51.5	23	16	26	13
Middle eastern	29 (20.3)	48.4	24	5	13	16
Indian subcontinent	63 (44)	32.8	45	18	34	29
South East Asian	12 (8.4)	32.7	3	9	7	5
Total	**143 (100)**	**41.0**	**95 (66%)**	**48 (34%)**	**80 (56%)**	**63 (44%)**

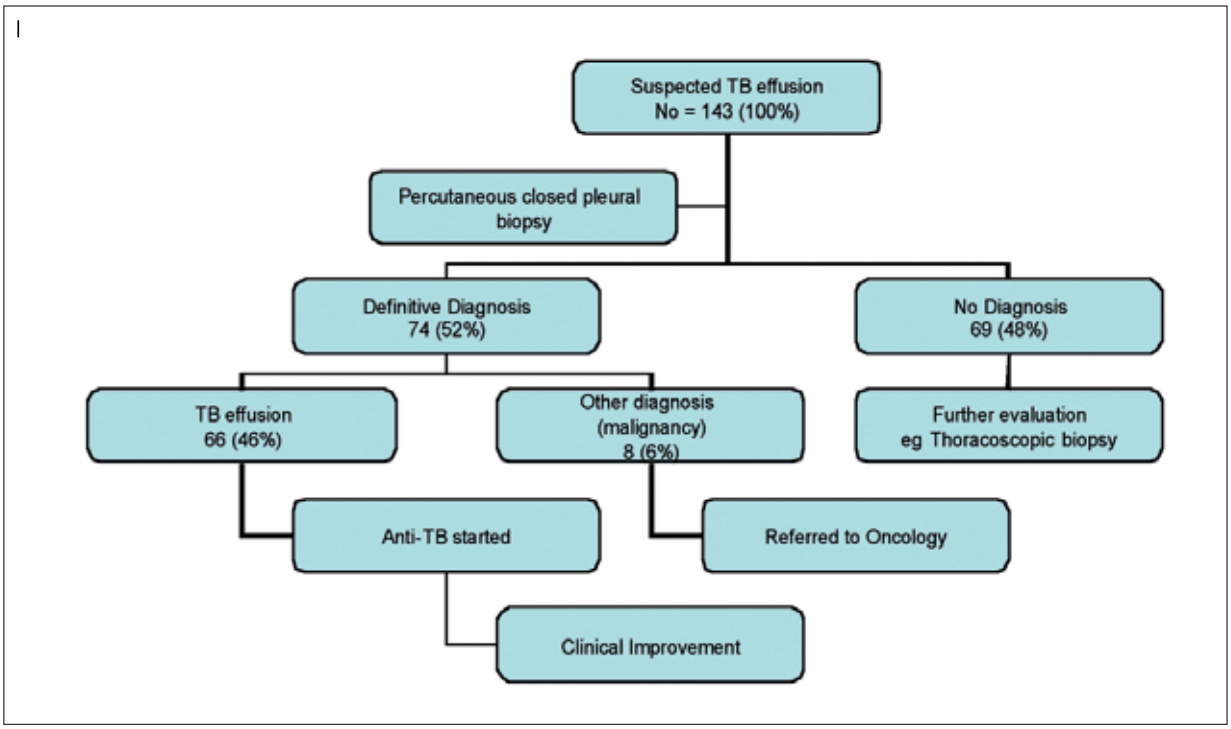

Figure 2 - Diagnostic yield of percutaneous closed pleural biopsy.

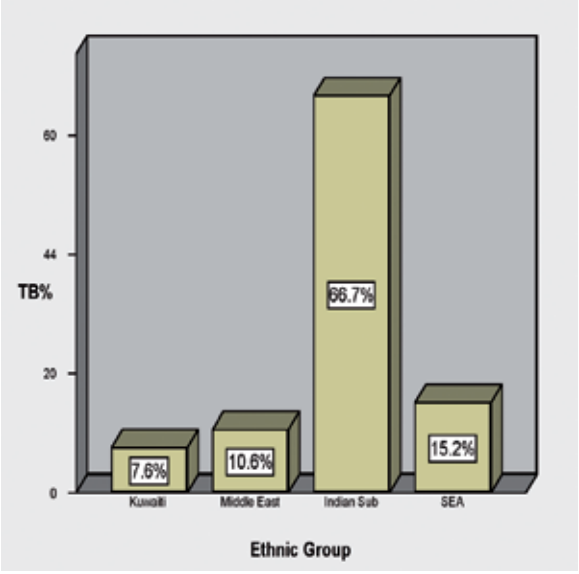

Figure 3 - Prevalence of TB pleurisy among different ethnic groups in Kuwait (n=66).

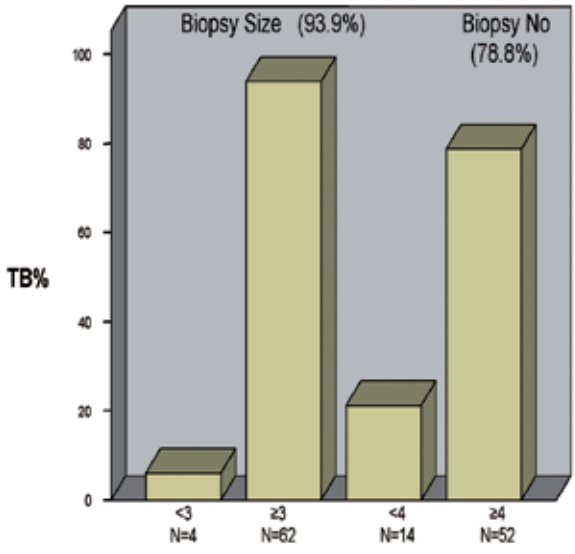

Figure 4 - Proportion of different groups of pleural biopsy sizes and numbers among cases with biopsy proven TB pluritis (n=66).

Table 2 - Association of the number and size of biopsies with the diagnostic yield of tuberculosis (TB) (N=143).

Diagnostic yield	No. of biopsies			Size of biopsies (mm)		
	< 4	≥ 4	*P*-value	<3	≥3	*P*-value
Definitive diagnosis (%)	15/42 (35.7)	59/101 (58.4)	0.013	6/21 (28.6)	68/122 (55.7)	0.021
TB (%) of total biopsies	14/42 (33.3)	52/101 (51.5)	0.047	4/21 (19.0)	62/122 (50.8)	0.007

is reportedly higher (299/100,000 as per WHO tuberculosis database 2006).[13] Analytically and duly supported by the previous studies, the optimal number of pleural biopsies needed to enhance the yield of TB pleurisy, and overall diagnostic yield was 4 samples (p=0.047 and 0.013), (**Table 2**). Mungall et al[15] arrived at similar conclusion in their study. Kirsch et al,[16] found a direct relationship between the number of specimens submitted, and sensitivity of pleural biopsy. In their 30 subjects, they found that more than 6 specimens were required to get the highest sensitivity (100%) of percutaneous needle biopsy for diagnosis of tuberculous pleurisy, as long as it contains 2 parietal pleura. This does not contradict our findings and others[15] of 4 large specimens. Jimenez et al[17] on the other hand, found that 4 specimens increased the diagnostic yield of percutaneous closed pleural biopsy for malignancy, but not tuberculous effusion. The mean age group of their study subjects was higher than in ours (64 versus 41 years), with lower tuberculous effusions (19%). Likewise, the size of pleural samples obtained, had an equal impact on the diagnostic yield. But, this may not always be feasible even by an experienced respirologist. The size factor was one variable that could not be controlled, except with the type of needle used (Abram's biopsy needle being the largest).[6] Therefore, a cut-off size of 3mm and above was proposed, being the size that most samples were centered around, adding to the fact that Abram's inner needle diameter with its hook permits having only few millimeters of pleural samples. In our study, we identified a statistically significant relationship between the overall diagnostic yield, and TB pleurisy on one hand with a size of ≥3 mm of pleural sample per case (p=0.021 and 0.007), (**Table 2**). Although, this conclusion makes pathologists content, it makes a respirologist job harder when performing the procedure, since it depends mainly on pure chance rather than experience, when using a standard biopsy needle to get larger samples. Furthermore, when reviewing only biopsy proven TB pleurisy cases, an overwhelming majority had a minimum of 4 samples and 3mm of pleural specimen size (78.8% and 93.9%), (**Figure 4**). This tends to confirm our hypothesis that number and size did matter when performing percutaneous closed pleural biopsy.

As a retrospective study, absence of follow up of those non-diagnostic samples was a limitation, fueling an argument concerning the number of missed TB pleurisy cases by percutaneous pleural biopsy, and diagnosed by other means, impacting on the exact accuracy of this tool. But the study effectively measured the frequency at which percutaneous pleural biopsy provided a definitive diagnosis out of total cases that had biopsy (that is, the diagnostic yield).

Percutaneous closed pleural biopsy is a simple, fast, and safe procedure that still remains a useful diagnostic tool, when medical or surgical thoracoscopy is not readily available for patients with suspected TB pleurisy. Obtaining a higher number of samples ≥4, and larger specimens ≥3 mm in size for histopathological evaluation, were associated with better diagnostic yield for tuberculous pleurisy. When larger samples of 3 mm and above are difficult to obtain, we recommend increasing the number of pleural biopsies to a minimum of 4 to enhance the diagnostic yield of tuberculous pleurisy.

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