Original Article

Diagnostic Yield and Safety of Closed Pleural Biopsy in Exudative Pleural Effusions

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Abstract

Introduction: Exudative pleural effusion is one of the most commonly encountered clinical conditions for pulmonologists. Sometimes, etiological diagnosis of pleural effusion is difficult despite cytological, biochemical, and microbiological tests and is then labeled as undiagnosed exudative pleural effusion (UPE). The present study aimed to assess the diagnostic yield and safety of closed pleural biopsy (CPB) in such patients with UPE. **Materials and Methods:** This was a hospital-based, interventional study conducted on 101 UPE patients for 2 years. All patients were subjected to CPB using Abrams needle. Pleural biopsy samples were subjected to histopathology, Ziehl–Neelsen staining, and tuberculosis (TB) culture. All the data, including demographic characteristics, pleural biopsy reports, and procedure complications, were recorded. Statistical analysis was performed using the SPSS software 10 and results were expressed in terms of means and percentages. **Results:** A total of 101 patients (68 males and 33 females with a mean age of 50.1 years) were subjected to pleural biopsy. Of 88 patients in whom adequate pleural tissue was obtained, diagnosis of malignancy and TB was made in 36 and 31, respectively, and pleural biopsy examination findings were nonspecific (acute/chronic inflammation) in 21 patients. The diagnostic yield of pleural biopsy was 76%. Minor complications were observed in ten patients. **Conclusions:** A pleural biopsy is a valuable diagnostic tool in UPE cases. Malignancy was the most common cause of exudative pleural effusion, followed by TB in our setup. Pleural biopsy should be considered in all patients with UPE.

Keywords: Exudative pleural effusion, malignancy, pleural biopsy, tuberculosis

Introduction

Exudative pleural effusion is one of the most commonly encountered clinical conditions for pulmonologists and physicians. Establishing an etiological diagnosis of exudative pleural effusion is essential to offer correct treatment. As many as, 15%–20% of all pleural effusions remain undiagnosed despite good history, appropriate blood investigations, and analysis of aspirated fluid.[1] We hereafter will refer to such cases as "undiagnosed pleural effusions or undiagnosed exudative pleural effusion (UPE)." Such patients tend to either receive empirical tuberculosis (TB) treatment (this being the most common cause of pleural exudates in India) or a "wait and watch" approach is adopted. This leads to a delay in diagnosis and also exposes the patient to adverse reactions to empirical TB treatment. The most efficient and cost-effective investigation in such patients is a matter of debate, especially when pleural tissue is required for diagnosis.[2] Pleural biopsy provides diagnostic evidence for both TB and malignancy, the two most important causes of exudative pleural effusions in India.[3] Closed pleural biopsy (CPB) is well established in the diagnosis of tuberculous pleuritis, in which the yield from microbial analysis of pleural fluid may be poor.[4] Before the availability of thoracoscopy, a CPB was the investigation of choice in patients with UPEs, and the diagnostic yield of pleural biopsy in such situations has been reported to be between 60% and 80%.[5,6] Thoracoscopy has a better yield than a pleural biopsy and is nowadays a preferred method of obtaining pleural tissue.[7] However, a CPB is an inexpensive technique with minimal complications and does not require great experience.[8,9]

The objective of the present study was to evaluate the role and safety of percutaneous parietal pleural needle biopsy in cases of

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UPE, as we felt the need to establish whether it still has a role to play in resource-limited settings and whether it should be considered ahead of thoracoscopy in the diagnostic algorithm.

Materials and Methods

This was a prospective, interventional study conducted in a tertiary care hospital for 2 years, from September 2018 to September 2020. The study was approved by the Institutional Review Board (IRB) (IRB approval number: DPU/R & R(M)/19/107/2019) and performed in accordance with the principles of the Declaration of Helsinki. Written and informed consent was obtained from all enrolled patients after explaining the study protocol in detail.

Patients with pleural effusion aged more than 18 years and who were able to understand the procedure were included in the study. Patients with minimal pleural effusions, bleeding diatheses or those taking anticoagulants, respiratory failure (both Type 1 and Type 2), and those with local skin infection (unsuitable for biopsy) were excluded from the study. Demographic details, clinical history, and physical examination of all patients were captured and entered in individual case record forms. Subsequently, thoracocentesis was done to obtain the pleural fluid for analysis.

In all the enrolled cases, the aspirated fluid was sent for (i) routine examination, which included total leukocyte count, differential leukocyte count, and red blood cell count, mesothelial cells, and malignant cells. (ii) Biochemical tests: Pleural fluid protein, lactate dehydrogenase (LDH), glucose, adenosine deaminase (ADA) (serum protein and serum LDH were measured too). (iii) Microbiological tests included Gram stain, Ziehl–Neelsen (Z-N) stain, solid culture for mycobacteria, aerobic culture, fungal stain, and Xpert MTB/RIF assay (CBNAAT cartridge-based nucleic acid amplification test). (iv) Other tests required to establish a diagnosis, such as pleural fluid and serum rheumatoid Antibody factor and antinuclear antibody, fluid triglyceride levels, computed tomography (CT) pulmonary angiography, and bronchoscopy were done whenever indicated and were case specific.

The patients whose definitive diagnosis could not still be established were labeled as UPE and were included in the study. They were subjected to CPB after obtaining separate informed consent.

Pleural biopsy protocol

All the study participants with UPE were subjected to CPB using Abram's needle [Figure 1] after explaining the procedure in detail and obtaining informed consent. The procedure of pleural biopsy was done as described by Light.[10] The site for biopsy was selected after careful clinical and radiological correlation. Ultrasound was done in cases with loculated pleural effusion to determine the appropriate biopsy site. This area was cleaned thoroughly with antiseptics and then infiltrated with local anesthetic (2% lignocaine). The needle was introduced through a small incision given just above the upper border of the rib at the selected site, and 4–5 biopsies were obtained from the parietal pleura. After biopsy, a skin incision was sutured with a single stitch, and a chest X-ray was done to rule out any complications such as pneumothorax. Pleural tissues were placed in three vials; one with 10% formalin for histopathological examination and others in normal saline for microbiological investigations that included CBNAAT, fungal stain, and mycobacterial culture. Postprocedure, patients were kept under close monitoring of vital signs for the next 6 h. Adverse events, if any, related to the procedure were recorded and were addressed to.

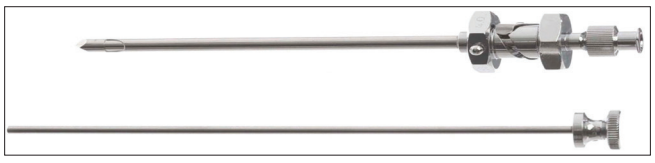

Figure 1: Abram's Pleural Biopsy Needle

Statistical analysis

Statistical analysis of the data was done using the SPSS version 10 (SPSS Inc owned by IBM, Chicago, USA), and results (findings) were expressed in terms of means, ratios, and percentages.

Results

Four hundred and sixteen patients of pleural effusion meeting the inclusion/exclusion criteria were included in the study. Thoracocentesis and subsequent pleural fluid investigations, including cytological, biochemical, and microbiological tests were able to establish diagnosis in 315 patients. The remaining 101 patients were labeled as UPE and were subjected to pleural biopsy. Of 101 study participants, 68 were male and 33 were female. The mean age was 50.1 ± 16.7 years. Fifty-six were smokers (52 males and 4 females). The most common presenting symptoms were fever (96%) followed by cough (91%), dyspnea (85%), and chest pain (82%). The duration of symptoms observed in study participants was <2 weeks in 21 patients, 2–6 weeks in 42, and more than 6 weeks in the remaining 37 patients.

A pleural tissue sample was inadequate in 13 patients; hence, they were excluded. An overall total of 88 cases was included in the final analysis. Of 88 patients, malignancy was established in 36 (41%) patients, TB in 31 (35%) patients, and the pleural biopsy was inconclusive (acute/chronic inflammation) in 21 (24%) patients [Table 1]. The most common type of malignancy observed in our study was adenocarcinoma (59% of patients), followed by squamous cell carcinoma in 10 (28%), mesothelioma in 2 (5%), small cell carcinoma in 2 (5%), and germ cell tumor in 1 (3%) patient [Table 2]. Out of 31 patients in whom TB was established, the histopathological examination showed epithelioid granuloma with caseous necrosis in 16 (50%) patients and epitheloid granuloma without necrosis in 9 (30%) patients. Pleural tissue was positive for

ZN staining in 3 (10%) and mycobacterial culture of pleural tissue was positive in three (10%) patients [Table 3]. Overall, a pleural biopsy was able to diagnose 67 out of 88 (78%) patients with UPE. Minor complications were recorded in 10 out of 100 patients that, included fever in 4 (4%), minor bleeding in 3 (3%), subcutaneous emphysema in 2 (2%), and pneumothorax in 1 (1%) patient. All patients with fever responded to antipyretics. Minor bleeding was managed by hemostasis and dressing. Subcutaneous emphysema in both patients resolved on the third postprocedure day after high-flow oxygen inhalation. Pneumothorax in one patient was very small and it resolved spontaneously on day three of procedure. Thirteen patients in whom the biopsy tissue was inadequate for any opinion were subjected for further evaluation which included radiology guided evaluation and thoracoscopy.

Discussion

Pleural effusion is one of the most common problems with which patients present to respiratory physicians. In the diagnostic workup of pleural effusion, thoracocentesis with laboratory analysis of pleural fluid is usually sufficient to establish an etiological diagnosis in the majority of cases. The diagnostic yield of pleural fluid analysis using pleural fluid ADA for diagnosing TB[11] is up to 92% while the diagnostic yield for pleural fluid cytology for diagnosing malignancy is around 60%.[7] In countries with a high prevalence of TB, differentiating TB from malignancy is extremely important since the cytology pattern of pleural fluid in early malignancy is similar to that of TB. It is a common practice to initiate empirical anti-TB treatment in cases of lymphocytic exudative pleural effusions, especially in rural and semi urban areas where other diagnostic modalities are not readily available or affordable. In such cases, an alternate diagnosis is considered only after a few months if there is no response to therapy. This leads to undue delay in the diagnosis. A simple and cost-effective percutaneous pleural biopsy which is seldom practiced nowadays needs to be revived.

Table 1: Pleural biopsy findings

Final diagnosis	Total patients	Males	Females
Malignancy	36	25	11
TB	31	17	14
Acute/chronic inflammation	21	12	9

TB: Tuberculosis

Table 2: Incidence of pleural malignancies

HPE	Frequency (n=36), n (%)
Adenocarcinoma of lung	21 (58.3)
Squamous cell carcinoma	10 (27.78)
Pleural mesothelioma	2 (5.56)
Germ cell tumor with lung metastasis	1 (2.8)
Small cell cancer of lung	2 (5.56)

HPE: Histopathological examination

Table 3: Diagnosis of tuberculosis on pleural biopsy

	Frequency (n=31), n (%)
Epithelioid granuloma with caseation necrosis	16 (50)
Epithelioid granuloma without necrosis	9 (30)
Pleural tissue positive for AFB staining	3 (10)
Pleural tissue positive for AFB culture	3 (10)

AFB: Acid-fast bacillus

CPB was first done by De Francis in 1955; Copes and Abram's needles are the most common CPB needles used.[12-14] CPB is part of the protocol for the identification of etiology in patients with lymphocytic exudative pleural effusion in our institution, although we have an image-guided pleural biopsy and medical thoracoscopy facilities available. The current study was undertaken to study the utility of CPB over the pleural fluid analysis in tubercular and malignant pleural effusion and to assess the safety of the procedure.

The diagnostic yield of pleural biopsy depends upon patient population, biopsy technique, number of biopsy specimens, and histopathological analysis.[15,16] Pleural biopsies can be done percutaneously, under image-guidance using ultrasound or CT, or under direct vision during thoracoscopy. Image-guided biopsy like ultrasound/CT greatly increases the yield of pleural biopsy. Thoracoscopy allows large volume thoracocentesis and direct visualization of the pleura. Multiple biopsies can be taken through a single insertion point, and, if necessary, talc poudrage can be performed to prevent recurrence of effusion. The overall diagnostic yield of CPB in our study was 78%. Studies done by Edmondstone.[17] and McLean *et al*.[18] reported the overall yield of CPB as 60% and 62%, respectively. The diagnostic yield of CPB in malignant pleural effusion in our study was 72% (36 out of 50 patients). In a study by Maturu *et al*.,[19] authors performed CPB in 84 patients, the yield of CPB was 84.5%, while Bhattacharya *et al*.[20] claimed the overall diagnostic yield of CPB to be 70%. Mungall *et al*.[21] obtained a diagnostic yield of 47% in malignant pleural effusion. The sensitivity for diagnosing TB in our study was 82% (31 out of 38) which is comparable to other studies that have ranges from 60% to 95%.[6,22,23] There were no major complications observed in study. Minor complications were recorded in 10% patients. Maturu *et al*.[19] also reported complication rate of 8% in their study.

CPB is well-recognized in the diagnosis of tubercular effusion in which the microbial yield of pleural fluid may be low. This is because TB affects the pleura diffusely, thus increasing the probability that diseased area will be sampled during closed biopsies.[3] However, the usefulness of CPB in the diagnosis of malignant effusion is less as compared to thoracoscopy.[18]

Definitive histological diagnosis in suspected malignant pleural effusion not only helps oncologists with appropriate treatment choices, but also offers valuable prognostic information. The experience and skill of the pathologist in the histopatological examination of pleural biopsy will also directly impact

the diagnostic accuracy of CPB, and this may differ from study to study and a health center to another.[24] The British Thoracic Society guidelines[25] in 2003, advised thoracoscopic pleural biopsy only after initial negative CPB. This needs to be reinforced. It seems appropriate to conduct CPB before opting for other procedures like image-guided pleural biopsy or pleuroscopy.[26]

Although the present study was not intended to examine economic aspects, the cost of image-guided pleural biopsy and thracoscopy (physician preparation and hospital stay) is substantial and not affordable to many. This is particularly relevant in areas with limited facilities or access to thracoscopy and other imaging facilities required for biopsy guidance. Although thoracoscopy allows direct visualization of the pleura thereby allowing multiple biopsies of pleura through a single-insertion point,[27] lack of technical expertise limits its usage in rural and suburban areas. Thoracoscopy also requires chest tube drainage, which further increases the hospital stay as well as the health care cost. In addition, the cost of procuring state of the art instruments and expertise required makes thoracoscopy or image guided biopsies expensive. On the other hand, pleural biopsy needles are cheap and can be done by relatively less experienced physician. Patient sedation is usually not required and the procedure is well tolerated, which allows tissue diagnosis in patients who are too sick to undergo more invasive tests. It is a bedside procedure and discharge from hospital is usually possible after only a short period of observation. Hence, CPB should be done in all the patients with exudative lymphatic pleural effusion.

Conclusion

In the diagnostic workup of pleural effusion, CPB provides high diagnostic yield in diagnosing of tubercular and malignant pleural effusion. It should always be considered as an initial diagnostic tool in the workup of UPE because of its low cost, easy availability, and low complication rates. The role of CPB in cases of exudative pleural effusion is still pivotal, particularly in places where the facilities of thoracoscopy are not easily available.

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Conflicts of interest

There are no conflicts of interest.

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