PLEURAL EFFUSION AND ROLE OF CLOSED PLEURAL BIPSY: A MIDDLE EASTERN PERSPECTIVE

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SUMMARY

Pleural effusions are common and can be caused by a wide variety of disease processes. The diagnosis of a pleural effusion can often be challenging when initial testing is negative. In Middle Eastern countries, tuberculosis and malignancy remain the most important considerations in patients with undiagnosed exudative effusions. Pleuroscopy (or thoracoscopy) is often considered the next step in the diagnostic process of these effusions. However, despite a higher diagnostic yield, there are several limitations including need for expertise, cost, invasiveness and lack of availability in some regions that restrict its widespread use. In these instances, closed pleural biopsy continues to be routinely performed. These procedures can increase the diagnostic yield compared to thoracentesis alone; more so in cases of tuberculosis compared to malignancy. We review various aspects of the closed pleural biopsy, including the differential yields in tuberculosis versus malignancy. We believe that there remains a valuable role for closed pleural biopsy, especially in regions with higher prevalence of tuberculosis, and that pulmonologists should be trained with the procedure until greater availability of pleuroscopy.

INTRODUCTION

Pleural diseases and effusions are commonly encountered in Middle Eastern countries (1-3). Sometimes the diagnosis of such effusions can be challenging, despite best efforts, especially in regions where advanced diagnostic techniques may not be widely available. Middle Eastern literature regarding the role of closed pleural biopsy (CPBx) and medical pleuroscopy in the evaluation of pleural effusion is limited. The purpose of this article is to review the literature regarding etiology of pleural effusions commonly encountered in the middle east, while clarifying the role of a CPBx.

'Middle East' comprises of several countries between far eastern Europe, western Asia, and Northern Africa. For the purposes of this paper, the term Middle East will include the 17 countries of Qatar, Saudi Arabia, United Arab Emirates, Yemen, Oman, Jordan, Syria, Lebanon, Israel, Iraq, Iran, Kuwait, Gaza strip, Turkey, Cyprus, Egypt and Bahrain (Figure 1).

METHODOLOGY

We sought to obtain an overview of published literature in relation to pleural effusions and pleural biopsies, that specifically focused on practices in one or more of the Middle Eastern countries defined above. Publications were in English from 1955-2011 and included original research, reviews, book chapters, editorials, abstracts and case reports.
PLEURAL EFFUSIONS

Definition - Pleural effusion refers to the abnormal increase in the amount of fluid in the pleural space. Approximately 0.1-0.2 mL/kg body weight per body side of pleural fluid is normally present (4). Disease processes that cause an imbalance between its formation and absorption may contribute to the accumulation of fluid. Greater than 175 mL of fluid is usually discernible in an upright chest x-ray (5).

Classification and Analysis

Pleural effusions are generally classified into two broad categories: exudates and transudates. The distinction between these 2 categories is usually the first step in the analysis of a pleural effusion. Light's criteria (6) are still being applied for this distinction. However, approximately 15-20% of transudative effusions are falsely identified as exudates based on this criteria, especially in cases of prior diuretic use (7).
Exudative Effusions-Mechanism of exudative effusion is increased capillary permeability due to disease of the pleura or adjacent tissues by infection or, inflammation. It also forms as a result of decrease in lymphatic drainage as in malignancy.

Tuberculosis (TB) - This is the most common cause of a pleural effusion in several Middle Eastern countries, where tuberculosis remains endemic. While some countries do not have published data, a few studies in other countries have conclusively shown the highest prevalence of tuberculous effusions compared to other etiologies - 32.5% out of 200 patients studied in Qatar (1), 35.2% (out of 253 patients) (8) and 37% (out of 201 patients) (9) in two studies from the eastern province of Saudi Arabia, 38% of 100 patients in Iraq (10) and 43.7% of 165 patients with exudative effusions in Lebanon (2). Another study estimated that the incidence of TB in Israel was approximately 500/year. (11). In contrast to this, data from 100 patients in Babol, Iran showed tuberculous effusions to be only the second common cause of exudative effusions (33% of cases), next to malignancy (12). Another Iranian study also showed that tuberculous effusions were less common than malignant and parapneumonic effusions (3). Some of the differences in various regions and countries might be attributable to the variations in pockets of endemicity, differences in immigration rates from other developing countries where TB remains endemic, variable lifestyle and socioeconomic and occupational risk factors.

Tuberculous effusion in these regions is seen more commonly in a younger population and is predominantly unilateral. Data from Qatar shows that 84% of the patients with tuberculous effusion were less than 45 years of age and the disease was mainly primary in nature, than reactivation (13). Lebanese data similarly, also shows that 66.7% of these patients were younger than 50 years of age (2). Tuberculous effusion typically occurs due to delayed hypersensitivity to tubercular protein. The effusion tends to be predominantly lymphocytic, with higher viscosity (14), with definitive diagnosis based on presence of acid fast bacilli in smears/culture or biopsy samples or positive PCR testing for TB DNA. Elevated markers including adenosine deaminase levels >45 IU/L, increased lysozyme (muramidase) and gamma interferon levels >140 pg/mL (15, 16) are typically found.

Malignancy - Malignant effusions are reported to be the most common cause of exudative pleural effusions in Iran (27.2%), and second only to congestive heart failure, when all effusions were considered (3), second most common in Iraq, 34% of all effusions (10), Lebanon, 32.1% of all exudative effusions (2) and Saudi Arabia, 18% of all effusions (9) and third most common cause in Qatar 15.5%, with TB and parapneumonic effusions being first and second respectively (1).

Middle Eastern data reveals that the most common cause of malignant effusions again varies between countries. In Qatar and Iraq (1,10), bronchogenic carcinoma was the leading etiology, whereas in Iran, metastatic cancers contributed to 95% of cases (12). Lung cancer however remains as the most common cause of primary malignancy with effusions. The incidence of malignant mesothelioma is higher in Turkey, given increased exposure to asbestos fibres (tremolite and chrysotile), naturally occurring fibre zeolite (or erionite), or due to familial or genetic predisposition in some cases (17). Environmental asbestos exposure contributing to mesothelioma was also noted in other Mediterranean regions, including Cyprus (18) as well as Egypt (19).
Other cancers that can also contribute to malignant effusions include breast, gastrointestinal, ovarian, lymphomas ( Hodgkins and non-Hodgkins, including primary effusion lymphoma), multiple myeloma, rib tumors etc.

Malignant effusions commonly occur due to lymphatic obstruction and pleural involvement with malignant tissue. Obstruction of a bronchus with atelectasis, post-obstructive pneumonia, involvement of thoracic duct (chylous effusions) and inflammation can cause paramalignant effusions (7). Effusions are termed 'paramalignant' if they are caused indirectly by cancer or are related to effects of chemo- or raditherapy, or other drugs (20). Malignant effusions, like TB, are also predominantly lymphocytic; they however, tend to occur more commonly in older patients. Fluid characteristics also show lower pH and glucose if the tumor burden is very high, and often, the presence of blood. LDH is generally elevated and an Israeli study suggested that LDH isoenzyme analysis may be helpful in the evaluation of a malignant effusion (21). A small percentage of patients with malignant effusions might have transudates instead of exudates, as reported by Gonlugur et al in a Turkish study (22). This is thought to be due to either atelectasis, early involvement of mediastinal nodes or simultaneous disease processes contributing to transudative effusions, such as congestive heart failure.

Since positive pleural fluid cytology is only obtained in approximately 50-60% of samples (23, 24), testing for tumor markers (including CEA, CA 15-3, CYFRA 21-1, CA 19-9, CA 125, MCA, NSE) has been evaluated to improve diagnostic yield. Shitrit et al in Israel found a higher diagnostic accuracy of pleural fluid CEA of approximately 85% for malignant effusions and recommends this be tested in patients with concern for malignancy (25).

Mesothelin, an antigen in mesothelial cells (and soluble mesothelin-related peptides, SMRP) has also been studied favourably as a tumor marker for mesothelioma, with increased levels in serum and effusions related to malignant mesothelioma (23,26-28). Osteopontin, a glycoprotein, and megakaryocyte potentiating factor (MPP) are also being studied as mesothelioma tumor markers.

Infections (other than TB) - Parapneumonic effusions commonly occur in association with bacterial or viral pneumonias, bronchiectasis, abscesses (lung, liver or other subphrenic) and hydatid disease (common in several middle eastern countries and endemic in Turkey, Egypt and Saudi Arabia) (29,30). In Qatar, parapneumonic effusions are the second most common cause of effusions overall (19%). In a Turkish study of pediatric patients, pneumonia was the etiology in approximately 77% of all effusions (31). Common bacteria implicated include Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae and Klebsiella pneumoniae (1,31).

Case reports from Middle East also report effusions caused by pleural involvement by brucella (endemic in Saudi Arabia), pyelonephritis, typhoid fever with splenic abscess, pleuropulmonary amebiasis, hepatitis A, etc as some of the less frequent infectious causes of pleural effusions (32-37).

Systemic diseases - Several rheumatologic and gastrointestinal disorders can contribute to exudative effusions. Gastrointestinal disorders causing effusions include pancreatitis, esophageal rupture or perforation, pancreaticopleural fistulas and post-operative effusions. Rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome, Churg-Strauss vasculitis and Wegener’s granulomatosis are the more common rheumatologic disorders associated with effusions. An Israeli case
pressure and/or decreased oncotic pressure, contributing to transudation of fluid into the pleural space. A Turkish study found that there are higher pleural fluid levels of a new biomarker, ischemia modified albumin (IMA), in transudates (50).

**Congestive heart failure (CHF)** - This is the most common cause of transudative effusions across the board. In the United States and other developed countries, as well as Iran, contrary to most other Middle Eastern countries, this is considered to be the most common cause of pleural effusions in general (3,51). Diagnosis is usually made by a combination of history, physical examination, laboratory data, including elevated brain natriuretic peptide (BNP) and pro-BNP values, as well as radiologic data. Pleural effusions are generally bilateral, but can be unilateral in some cases. Thoracentesis is usually not performed for the typical CHF patient unless effusions are large, persistent or the patient has other signs or symptoms suggestive of an additional underlying process. When performed, effusions are almost always transudative. However, in some cases, especially after acute diuretic therapy, fluid can appear to be exudative, owing to fluid movements in excess of LDH and protein out of the pleural space (52). Chronic diuretic therapy, in contrast, does not appear to significantly change fluid classification.

**Miscellaneous causes** - This includes several other causes of pleural effusions, including pulmonary embolism (with 20-40% of diagnosed patients reportedly having an effusion) (7), drug-induced (nitrofurantoin, amiodarone, valproic acid, bromocriptine, etc), ovarian hyperstimulation, yellow nail syndrome, post-coronary bypass grafting, drowning and post-lung transplantation (effusions are neutrophilic soon after surgery and predominantly lymphocytic in later postoperative periods) (39). Middle Eastern literature also includes cases of silicosis, autoimmune endocrinopathy, familial lymphedema, angiotensin-converting enzyme inhibitor (cilazapril) and extramedullary pleural hematopoiesis contributing to miscellaneous causes for exudative effusions (40-44).

Eosinophilic effusions (EPEs) are a subtype of exudative effusions, where the eosinophil content of the effusion is >10% and generally occur in 5-15% of pleural effusions. These are nonspecific and can occur due to several causes-malignancies as well as benign conditions including infections, parasitic diseases, pancreatic disease, pulmonary embolism, autoimmune disease, sarcoidosis, drugs, following multiple thoracentesis, pneumothorax, trauma, etc or they may be idiopathic (45).

A Turkish study of EPEs in 60 patients demonstrated benign etiology in 43.3% of cases, malignant/paramalignant etiology in 36.7% and idiopathic in 20% (46).

Other miscellaneous causes of EPEs per Middle Eastern case reports include autoimmune endocrinopathy type 2, hydatid disease, valproic acid or propylthiouracil use and end-stage renal disease with fibrinous pleuritis (29,41,47-49).

**Transudative Effusions** - Mechanism of effusion is due to increased vascular hydrostatic pressure and/or decreased oncotic pressure, contributing to transudation of fluid into the pleural space. A Turkish study found that there are higher pleural fluid levels of a new biomarker, ischemia modified albumin (IMA), in transudates (50).
transudative). There are case reports of urinothorax, including an Israeli case report (53), contributing to pleural effusion. In urinothorax, urine is present in the pleural space, mainly due to obstructive uropathy or after urologic procedures.

**DIAGNOSTIC EVALUATION**

Several studies have shown that the diagnostic yield of thoracentesis alone varies from approximately 25-75% (54-56) for pleural fluid cultures in tuberculosis and generally 40-87% for malignancy (57, 58, 59). The wide variation in detection of AFB in pleural fluid is thought to be due to the presence of only small numbers of organisms since the effusion is caused due to delayed hypersensitivity reaction (56). The variation in cytological detection of malignant cells in pleural fluid can be attributed to some extent on the type of cancer, the mechanism of its production, and presence or absence of visceral pleural involvement (60,61). Pleural fluid cytology has much higher diagnostic yield in malignancies such as adenocarcinoma of the lung and metastatic ovarian/breast cancer than squamous cell lung cancer, sarcoma, mesothelioma or Hodgkins lymphoma, on this grounds (56,62,63). While there is some conflicting data on the optimal amount of fluid required for the diagnosis of malignancy and whether such a threshold even exists (57,64,65), one study reports an advantage of repeat thoracentesis, with increased yield of 27% the second time and 5% the third time (66). The patients with negative thoracentesis often require additional tests for establishment of a definitive diagnosis. While physicians with access to advanced technology tend to proceed with thoracoscopy if thoracentesis has a negative yield, closed pleural biopsies continue to be commonly performed in Middle Eastern and developing countries. The procedure is usually performed at the same time as the initial thoracentesis.

We explore the various aspects of the closed pleural biopsy and classify its role in this region, especially amongst other diagnostic methods in the current era of technological advancement.

**CLOSED PLEURAL BIOPSY**

**HISTORIAL PERSPECTIVE**

The technique of closed pleural biopsies using a needle was first described by De Francis, Klosk and Albano in 1955 using Vim Silverman’s needle (cutting/puncture type needle) (67). However, as noted in a couple of studies between 1957-1960, upto 27-29% of samples obtained by the Vim Silverman needle were inadequate, and there was a need for improved techniques (68). In 1958, Abrams popularized the use of a Harefield needle (punch biopsy needle, now called Abrams needle) (69) and Cope popularized a hook type needle (70).

These needles continue to be used for closed pleural biopsies to this day and have been found comparable in terms of the diagnostic yield (71,72); however, certain individual advantages to each needle and biopsy technique remain. The Abrams needle is felt to be superior in providing larger quantity of tissue, improved mesothelial sampling, and greater cutting surface; while the Cope needle is felt to be advantageous due to the ability to take biopsies in presence of minimal amounts of pleural effusion (71,73).

In 1989, McLeod introduced the tru-cut needle, a cutting needle mainly used for biopsies of solid organs/nodes and lesions, for biopsies of the pleura and proved it to be a safe alternative to Abrams needle, especially in circumstances where there was a moderate to large effusion in presence of pleural
Data from the Middle East also support these results with regards to malignancy (82-84); although there is a higher diagnostic yield for tuberculosis where the disease is prevalent. A study from Egypt (85) demonstrated that PCR testing of the pleural biopsy specimen for Mycobacterium tuberculosis DNA, has a sensitivity of 90%, comparable to pleural biopsy cultures using BACTEC culture medium (92.3%). The yield of histopathologic exam was comparatively lower at 53.8% and Ziehl-Neelsen AFB staining alone in biopsy specimens had much lower sensitivity of 3.8%.

Table 1 lists several Middle Eastern studies with data on individual diagnostic yield of closed pleural biopsies for tuberculosis and malignancy as well as complications.

**INDICATIONS**

Closed pleural biopsy is generally performed in cases of exudative effusions that remain undiagnosed after a diagnostic thoracentesis, especially when tuberculosis or malignancy is suspected (15,51).

Simply stated, during a closed pleural biopsy, the needle is inserted into the pleural space after local anesthesia and multiple samples of parietal pleura are obtained. An 'adequate' specimen is typically one comprising of intercostal muscle next to gray or white parietal pleura (78). Technique of obtaining pleural biopsy are well described elsewhere (69,70,73,77,79,80).

**DIAGNOSTIC YIELD OF PLEURAL BIOPSY**

In tuberculosis, pleural biopsy is generally felt to be diagnostic in approx. 50-80% of cases (58) and some studies report upto 90% sensitivity with 99% specificity (81). In malignancy, diagnostic yield is approximately 40%-60% (58,78).

Cytology is less sensitive than CPBx in cases of TB whereas it is more sensitive than CPBx in cases of cancer due to less involvement of costal parietal pleura in several patients with malignant effusions (58). However, it is well understood that the yield of combination of thoracentesis and CPBx is significantly higher for both conditions (86) (Table 1). For tuberculosis, the yield from sputum culture,
pleural fluid testing as well as histopathology from CPBx increases the yield up to 85-90% by one report (86). In other reports, combined biopsy and pleural fluid evaluation, has a yield of up to 95% for TB (87) but lower at 74% for malignancy (88). Such a high yield in tuberculosis is similar to data from thoracoscopy. Therefore one could argue that in cases of suspected tuberculosis, pleural biopsy and thoracentesis are sufficient, and thoracoscopy may not add further significant benefit.

**FACTORS INFLUENCING DIAGNOSTIC YIELD**

The yield of the CPBx is dependant on several factors (89,90):

- Disease characteristics - including mechanism and site of pleural involvement, and stage of cancer.
- The variation in diagnostic sensitivity in cases of tuberculosis versus malignancy is in part due to the difference in the nature of pleural involvement in different disease states. In tuberculous pleuritis, involvement of the pleura is more disseminated and uniform, increasing the yield of a pleural biopsy (91). It is sufficient to prove the presence of granulomas (77), even without positive AFB smears. However, in malignancy affecting the pleura, the involvement is often more patchy (86) in the parietal pleura with early metastatic lesions often affecting the visceral pleura initially (84). Since the pleural space...
is not visualized in the closed blind biopsy, the sample obtained from the parietal pleura may not contain malignant lesions and may subsequently be non-diagnostic, decreasing the overall yield (92). A previous study of 272 biopsies has also shown that a strong limitation in the yield of biopsies was the accuracy of sampling site (93). Needless to say, the more advanced the stage of cancer with greater involvement of pleura, the higher the diagnostic yield of the biopsy is. Since patients with malignancy can also have paramalignant effusions, without direct malignant pleural involvement, a pleural biopsy in these patients can often fail to yield a diagnosis (20).

B) Technical Factors – Besides the type of needles used (Vide supra), size and adequacy of the diagnostic sample, number of locations sampled and specimen obtained also influence the diagnostic yield.

There has been several studies looking at optimizing diagnostic yield of CPBx with varying number of biopsies and sample size. There does not appear to be a consensus in number of biopsies required to optimize the diagnostic yield. For tuberculous pleuritis, it has been stated that if at least 3 specimens of pleural biopsy are obtained and cultures performed, the diagnostic yield for tuberculosis can be as high as 90% (77). A recent Kuwaiti study (94) showed that at least 4 biopsy samples with a size of at least 3mm significantly increases the diagnostic yield for tuberculosis; however the diagnostic yield overall was reported to be only 52% in 143 patients studied. Mungall et al showed improved diagnostic yield with multiple (upto 10) biopsies performed through the same site during a single procedure - with 88% rate for tuberculosis and 72% for malignancy. (95). Another prospective study (90) showed that a single sample of good quality is adequate for the diagnosis of TB, but recommended obtaining 4 samples when other conditions including malignancy are suspected; the diagnostic yield increased from 54% with one sample to 89% from 4 samples due to scattered pleural involvement with malignancy. Repeating pleural biopsies over time in malignancy may increase the diagnostic yield by only 2-4% (96).

Operator experience

As with any procedure, it is intuitive that the greater the experience, higher the likelihood of ensuring appropriate technique and sampling, and minimizing complications. However, pleural biopsies are easy to learn and perform, and can be obtained by specialists, non-specialists and trainees. (97). In one study (98), it was noted that all levels of physicians were able to safely perform pleural biopsies. In the United States, it is suggested that competency in pleural biopsies only requires knowledge of thoracentesis with an initial 5 procedures under supervision, with 5 subsequent procedures per year to maintain competency (99).

The experience of the pathologist interpreting the pleural biopsy sample is also a factor in determining the diagnostic yield.

There has been several studies, attempts and development of additional techniques to increase the yield of CPBx.

An Iranian study (100) introduced the method of closed percutaneous pleural brushing, with diagnostic yield of brushing higher at 91% than either cytology (67%), biopsy (58%) or the combination of cytology and biopsy at 79%. However, the diagnostic yield of brushing did not meet statistical significance compared to the combination of cytology and biopsy. The benefit of brushing was thought to be due to ability to obtain cells from greater areas of both parietal and visceral pleura in
The advantages of US guided biopsy include improved diagnostic sensitivity compared to conventional CPBx, improved characterization of both the effusion as well as pleural abnormalities (thickening, nodules and tumors) as well as improved availability even at bedside, ease of operation and lack of radiation.

The advantages of CT guided biopsy include improved diagnostic yield and improved visualization of areas not well seen on US. However, it is more expensive, requires assistance of radiologists and may have a longer waiting time for testing (63).

However, CT and US guidance may have limited availability in certain areas and add to increasing overall expenditure.

In malignancy, false positive biopsy results can rarely occur when reactive mesothelial cells are mistakenly thought to be malignant; especially in hemorrhagic effusions or infarction (89). False negative results can be seen in more longstanding or recurring effusions, when the sampling site has been altered by fibrosis, therapy, inflammation or other changes (89) and also in inaccuracies in sampling of affected pleural sites, as discussed in greater detail previously. Therefore, a negative or nonspecific result does not reliably exclude malignancies (81,93).

A Turkish case report mentions a case of false positive pleural biopsy for malignancy twice in a young patient with SLE due the presence of atypical mesothelial cells (104).

In tuberculosis, false positives can occur with nontuberculous granulomas (81).

Role of image-guided percutaneous pleural biopsies

Computed tomography (CT) or ultrasonography (US) guided CPBx have increased diagnostic yield compared to the conventional pleural biopsy (90). This is especially useful in pleural malignancies when nodules are present that can be targeted, improving the yield (89). CT guided closed pleural biopsy was noted to increase diagnostic yield of malignant mesothelioma in a Turkish study by Metintas et al (105), although complications of hemorrhage and pneumothorax were noted. In another more recent study by the same author (106), CT-guided Abrams biopsy was shown to have an overall sensitivity of 87.5%, compared to 94.1% with thoracoscopy and a higher sensitivity of 95% when pleural lesions were >1cm, which was comparable to 96% with thoracoscopy. Overall, image-assisted closed biopsy is felt to have a higher yield if there is pleural nodularity, thickening of more than 10mm, mass lesions of more than 20 mm in size and if the lesion is solid in nature (62).

Complications

Closed pleural biopsies are generally considered to be safe (78). However, the complication rate can be as high as 11-15% (15,63). Common complications include pain at the site of
procedure, pneumothorax (although not all cases require intervention), bleeding and vasovagal reactions. If thoracentesis and pleural biopsy are performed several times, pleural adhesions may occur (86) (Table 1).

**MEDICAL PLEUROSCOPY**

Medical pleuroscopy (MP) is increasingly considered to be the diagnostic procedure of choice in many countries in the evaluation of undiagnosed pleural effusions after unrevealing initial testing. MP can be performed under local anesthesia with direct visualization of the pleura and diagnostic yield has been shown to be similar to that of thoracotomy (107). Studies have shown that in appropriately selected patients with high suspicion for malignancy, sensitivity and specificity of MP were as high as 94% and 100% respectively (108). MP is also preferred in patients without pleural lesions on CT scan to guide biopsy and in large, recurrent effusions requiring drainage and pleurodesis. (109). An Egyptian study (84) showed the highest yield of 94% with MP and second highest yield of 84% from pleural lavage cytology, with only one patient having additional diagnosis with pleural lavage, increasing the combined yield to 96%. It was therefore proposed that pleural lavage with MP in suspected malignancy may be a good option to increase the yield. Diagnostic yield of MP was also high at 93% in cases of tuberculous pleuritis.

Other advantages of MP include ability to complete pleural staging in cases of malignancy in addition to other therapeutic procedures including pleurodesis.

**DIAGNOSTIC ALGORITHM FOR THE MANAGEMENT OF PLEURAL EFFUSIONS**

Figure 3 A-B: depicts a suggested diagnostic algorithm for management of effusions in the Middle Eastern Regions, where the prevalence of TB is generally high and where more advanced procedures such as MP may not be universally available.

Some authorities (7) recommend chest CT as the initial diagnostic method to rule out pulmonary embolism, pulmonary infiltrates, pleural masses, etc. However, we suggest that in cases with high suspicion for TB and in high-prevalence areas, initial testing with thoracentesis and CPBx might yield a diagnosis without requiring additional testing.

Since the yield of thoracentesis and pleural fluid cultures are lower than that of biopsy in cases of TB, it seems reasonable to proceed with both tests together at the same time. In cases of suspected malignancy, however, it is reasonable to perform thoracentesis first due to higher diagnostic yield of cytology, and if cytology is negative, then proceed with repeat thoracentesis along with pleural biopsy. However, the yield of conventional CPBx is invariably lower in malignancy when pleural fluid analysis is negative.

Approximately 15-20% of exudative effusions will remain undiagnosed despite extensive testing (4,59,77,91). Many of these effusions tend to resolve spontaneously (58). It is thought that approximately 75-80% of patients without definitive diagnosis after pleural biopsy will have eventual resolution of their effusion, while approximately 20-25% will be diagnosed with malignancy, usually within 2 years. The likelihood of malignancy in these patients with a nondiagnostic biopsy is considered to be higher than the likelihood of tuberculosis (110). In the study by Nusair (102), approx. 33% of patients with initial nondiagnostic pleural biopsies were ultimately diagnosed to have malignancy. If a patient with undiagnosed effusion appears to be clinically improving and there is no clinical suspicion for malignancy, it is reasonable to continue observation (58).
In patients with undiagnosed and untreated tuberculous effusion/pleuritis, there is an increased risk of up to 70% of developing active pulmonary or extrapulmonary tuberculosis in 5 years (86). It is suggested that if the second thoracentesis with cytologic examination and pleural biopsy are negative, then repeating these tests shortly after initial negative testing tends to be generally nondiagnostic and is not recommended (86). It is recommended that after non-diagnostic conventional CPBx, image-guided biopsy or pleuroscopy should be considered (98). If CT scan does not reveal any abnormalities - then pleuroscopy is recommended.

CONCLUSION

Pleural effusions are a commonly encountered clinical problem. Despite appropriate work-up, it is estimated that no diagnosis is established in approximately 15-20% of pleural effusions.

Several studies have shown that the diagnostic yield of thoracentesis alone varies from 30-70%, even when the prevalence of the disease is high. Advanced techniques such as pleuroscopy or thoracoscopy have a higher diagnostic accuracy at the cost of being somewhat more invasive, having a need for greater expertise and experience, and with limited availability in some regions. Closed pleural biopsies continue to have value, despite its limitations, especially in regions with higher prevalence of TB. It has several advantages including low morbidity, ease of the procedure, ability to perform at the time of initial thoracentesis at the bedside. Procedure is also easy to learn. In many studies, it has been proven that the combination of thoracentesis and closed pleural biopsies increases the diagnostic yield of exudative pleural effusions substantially, more so in cases of tuberculosis compared with malignancy. Despite recent technological advancement, closed pleural biopsies continue to be performed in the Middle East. Until medical pleuroscopy becomes available throughout the Middle East region, pulmonologists should be trained in closed pleural biopsy procedures.

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